University of New Hampshire
University of New Hampshire Scholars' Repository

Doctoral Dissertations | Student Scholarship

Summer 1973

THE SYNTHESIS AND STEREOCHEMISTRY OF SOME NITROGEN HETEROCYCLES

DAVID ALLAN WALSH

Follow this and additional works at: https://scholars.unh.edu/dissertation

Recommended Citation
WALSH, DAVID ALLAN, "THE SYNTHESIS AND STEREOCHEMISTRY OF SOME NITROGEN HETEROCYCLES" (1973). *Doctoral Dissertations*. 1028.
https://scholars.unh.edu/dissertation/1028

This Dissertation is brought to you for free and open access by the Student Scholarship at University of New Hampshire Scholars' Repository. It has been accepted for inclusion in Doctoral Dissertations by an authorized administrator of University of New Hampshire Scholars' Repository. For more information, please contact nicole.hentz@unh.edu.

INFORMATION TO USERS

This material was produced from a microfilm copy of the original document. While the most advanced technological means to photograph and reproduce this document have been used, the quality is heavily dependent upon the quality of the original submitted.

The following explanation of techniques is provided to help you understand markings or patterns which may appear on this reproduction.

1. The sign or "target" for pages apparently lacking from the document photographed is "Missing Page(s)". If it was possible to obtain the missing page(s) or section, they are spliced into the film along with adjacent pages. This may have necessitated cutting thru an image and duplicating adjacent pages to insure you complete continuity.

2. When an image on the film is obliterated with a large round black mark, it is an indication that the photographer suspected that the copy may have moved during exposure and thus cause a blurred image. You will find a good image of the page in the adjacent frame.

3. When a map, drawing or chart, etc., was part of the material being photographed the photographer followed a definite method in "sectioning" the material. It is customary to begin photoing at the upper left hand corner of a large sheet and to continue photoing from left to right in equal sections with a small overlap. If necessary, sectioning is continued again — beginning below the first row and continuing on until complete.

4. The majority of users indicate that the textual content is of greatest value, however, a somewhat higher quality reproduction could be made from "photographs" if essential to the understanding of the dissertation. Silver prints of "photographs" may be ordered at additional charge by writing the Order Department, giving the catalog number, title, author and specific pages you wish reproduced.

5. PLEASE NOTE: Some pages may have indistinct print. Filmed as received.

Xerox University Microfilms
300 North Zeeb Road
Ann Arbor, Michigan 48106

74-7023

WALSH, David Allan, 1945-
THE SYNTHESIS AND STEREOCHEMISTRY OF SOME NITROGEN HETEROCYCLES.

University of New Hampshire, Ph.D., 1973
Chemistry, organic

University Microfilms, A XEROX Company, Ann Arbor, Michigan

THIS DISSERTATION HAS BEEN MICROFILMED EXACTLY AS RECEIVED.

THE SYNTHESIS AND STEREOCHEMISTRY OF SOME NITROGEN HETEROCYCLES

by

DAVID ALLAN WALSH

B.S., Clarkson College of Technology, 1967

M.S., University of New Hampshire, 1970

A THESIS

Submitted to the University of New Hampshire

In Partial Fulfillment of

The Requirements for the Degree of

Doctor of Philosophy

Graduate School

Department of Chemistry

August, 1973

This thesis has been examined and approved.

Thesis director, Robert E. Lyle, Jr., Professor of Chemistry

Gloria G. Lyle, Associate Professor of Chemistry

James D. Morrison, Professor of Chemistry

Charles W. Owens, Associate Professor of Chemistry

Edward K. Tillinghast, Associate Professor of Zoology

August 8, 1973
Date

ACKNOWLEDGEMENTS

The author would like to express his appreciation and thanks to his advisor, Dr. Robert E. Lyle, for suggesting the thesis problem and for his advice, encouragement, and enthusiasm during all stages of the research. He would also like to thank Dr. Gloria G. Lyle for her aid in the development of this thesis manuscript.

To Dr. Alexander Amell and the other members of the Faculty and Staff of the Department of Chemistry, the author wishes to express his gratitude for their cooperation, assistance and instruction.

The author would like to extend his thanks to the University of New Hampshire for the educational opportunity which has been provided and for financial support in the way of a Teaching Assistantship, a UNH Graduate Teaching Assistant Summer Fellowship, an NDEA Title IV Fellowship (#69-019652), a UNH Dissertation Year Fellowship, and a Summer Tuition Scholarship. The author also wishes to express appreciation to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a PRF Research Assistantship from grant PRF 3441-A1,4.

Finally, the author would like to thank his many colleagues who aided in the recording of the nuclear magnetic resonance spectra.

This thesis is dedicated to my wife, Judy,

and to my daughters, Alicia and Karyn.

TABLE OF CONTENTS

Page

Page

LIST OF TABLES

LIST OF ILLUSTRATIONS

ABSTRACT

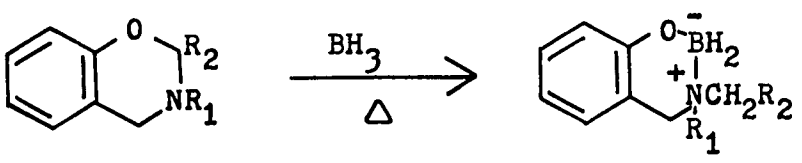
THE SYNTHESIS AND STEREOCHEMISTRY OF
SOME NITROGEN HETEROCYCLES

by

DAVID ALLAN WALSH

In order to investigate the consequences of intramolecular charge transfer interactions on inversion about nitrogen, a number of nitrogen heterocyclic systems was synthesized and studied. A series of 2-benzyl-1,2,3,4-tetrahydroisoquinolines were prepared and an intramolecular charge transfer band was observed in the uv spectrum of 2-(2',6'-dichlorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.

A series of 3,4-dihydro-1,3,2H-benzoxazines were synthesized. No intramolecular charge transfer could be observed for this ring system; however, a novel rearrangement to the [4H]-1-oxa-3-azonia-2-boratanaphthalene ring system occurred when the benzoxazines were treated with diborane.



An improved synthesis of pavinane alkaloids was developed using high dilution techniques. Several pavinane analogs were synthesized and these analogs had no observable intramolecular charge transfer bands in their uv spectra. Protonation of the pavinane alkaloids gave two isomers. It was determined from the nmr and uv spectra of the proton salts that the conformation in which the aryl nitrogen substituent was in a face-to-face orientation with the aromatic groups of the pavinane ring system was unfavored.

INTRODUCTION

> A molecule that contains a tricoordinate atom whose stable position is not within the plane defined by the three atoms directly bonded to it may, in principle, exist in two conceptually distinct conformations which are related by a transposition of the tricoordinate atom from one side of the plane to the other side. Such a molecule is described as being pyramidal, and pyramidal inversion is defined as any process that effects the interconversion of the two conformations.[1]

The inversion of the nitrogen pyramid in amines is well known. Classically, it proceeds via a coplanar arrangement of groups about the nitrogen center by a change in the hybridization of the nitrogen atom from sp^3 to sp^2. Nonclassically, inversion can occur by quantum mechanical tunneling.[2] In practice, however, tunneling is an important consideration only when at least one of the atoms bound to nitrogen is hydrogen or deuterium. This process becomes increasingly unlikely as the mass of the substituents on the nitrogen increases.

Barriers to this pyramidal inversion in tertiary amines may be considered as useful probes for understanding structural effects in organic molecules. Although the inversion rate of the two trigonal forms of a tertiary amine is too rapid to be detected by chemical means, the process may be slowed down by several methods: a) by including the nitrogen in a strained cyclic system; b) by linking electronegative heteroatoms to the nitrogen atom; c) by protonating the nitrogen to give a salt; d) and by cooling the system sufficiently to permit detection of inversion. Once inversion has been slowed, the rate of inversion can be measured

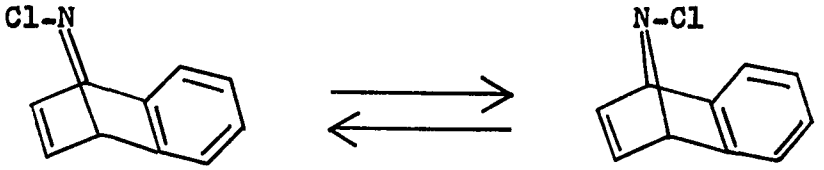
by physical methods, usually nuclear magnetic resonance spectroscopy (nmr).

The inversion barrier is much higher in aziridines[3] and azetidines[3a] than in the unstrained pyrrolidines and homopiperidines.[3b] In the planar transition state, the nitrogen is sp^3-hybridized so that the bond angle must increase to 120° during the inversion. When the nitrogen is incorporated in a small ring, however, the necessary increase in bond angle is hindered.

Steric acceleration of the rate of inversion in N-alkylaziridines has been confirmed by several studies.[3d,3e,4,5] Barriers of inversion of aziridines decrease in the order of increasing steric requirement of the substituent on nitrogen: $CH_3 < C_2H_5 < \underline{i}\text{-}C_3H_7 \ll \underline{t}\text{-}C_4H_9$.[3e,5]

Electronegative substituents also slow inversion at nitrogen. The effects of heteroatomic substitution and angular constraint on the barrier to inversion are compounded in N-haloaziridines, and in some cases invertomers have been separated.[1] This "hetero effect" could have two causes: a) as the electronegativity of the substituents increases, so does the s character of the lone pair of electrons on the nitrogen,[6] with the result that the energy difference for the transition state increases; b) the transition state is destabilized by the mutual repulsion of the lone pairs of electrons on the nitrogen and on the hetero atom. The inversion barrier in 1 was large enough ($\Delta G^{\ddagger}$ = 23.5 kcal/mol) to be measured by direct kinetics.[7]

Unsaturated substituents strongly depress the



1a 1b

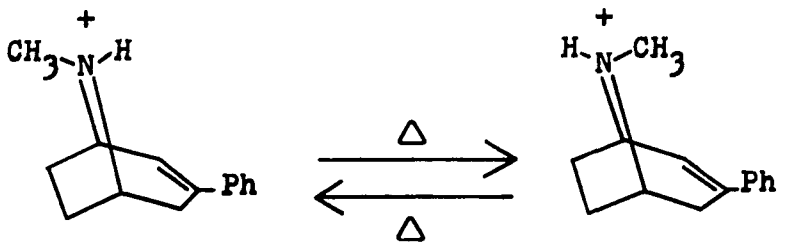
inversion barrier. During inversion, the hybridization of the bonding orbitals may be qualitatively regarded as changing from sp^3 to sp^2, and that of the lone pair of electrons from sp^3 to p. Any factor which favors the rehybridization process such as π delocalization of the lone pair, tends to flatten the pyramid and thus to lower the barrier to inversion. This effect rationalizes the observation that an adjacent aryl group lowers the barrier to inversion at nitrogen, presumably by a conjugative mechanism.[8]

When nitrogen is protonated, the barrier to inversion is greatly increased. In order for inversion to occur, the sp^3 hybridized nitrogen must rehybridize through a planar transition state. The energy required for this process is much larger for a protonated nitrogen than for the unprotonated form. The two signals for the nitrogen substituent have been observed by nmr for many tertiary methyl amines in acidic media.[9]

Saunders and Yamada[10] studied the rate of nitrogen inversion in dibenzylmethylamine (2) by introducing competitive equilibration of salt formation with a proton. These

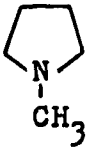
authors found that the rate of loss of a proton from the salt to the solvent or to the amine was more rapid than the inversion of the configuration of the amine nitrogen. Simmons and Park[11] have shown that the conformational isomers of the salts of macrobicyclic diamines with bridgehead nitrogen atoms could be isolated and showed a definite stability in aqueous media at room temperature. These results promised the possibility of the detection of two diastereomeric proton salts of tertiary amines which would differ only in the configuration of the nitrogen if: a) protonation of the tertiary amine produces the stereoisomers in a ratio different from the thermodynamic or equilibrium mixture; b) the free energy difference between the two isomers is sufficiently small for detectable amounts of both isomers to exist at equilibrium; and c) the isomers differ in some property which provides a probe for investigation of the mixture.

Lyle and Ellefson[12] were the first to provide an example of two diastereomeric ammonium salts which differ only in configuration of the nitrogen and are stable in solution at room temperature. They isolated two stable isomers of 3-phenyltropidine hydrobromide (3).

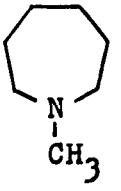


3a 3b

Bushweller and O'Neil determined[13] the barrier to inversion in unprotonated dibenzylmethylamine (2) to be 6.0 ± 0.5 kcal/mol. By cooling 2 to -146° using chloroethylene as solvent, they observed an AB quartet for the benzyl signal in the nmr spectrum, thus indicating slow inversion about nitrogen. Lambert[3b] also used this method to determine the barriers to inversion in N-methylpyrrolidine (4) and N-methylhomopiperidine (5).



4

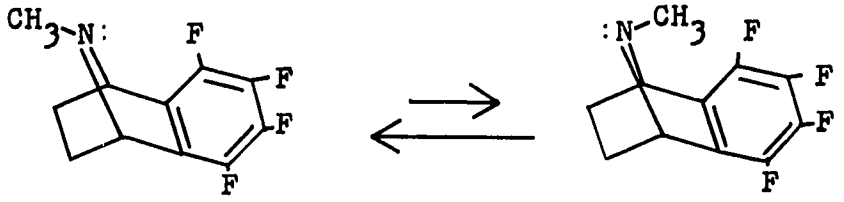


5

The objective of this thesis was to design specific chemical systems to study inversion about nitrogen in order to answer conformational questions not readily approachable by other methods.

One question under consideration was whether or not intramolecular charge transfer interactions could influence the energy barrier of nitrogen inversion. Gribble[13] has found in certain 7-azabenzonorbornadienes (6) that below the coalescence temperature, the invertomer that is favored has the nitrogen lone pair of electrons over the electron deficient aromatic ring. He suggests that there is an intramolecular charge transfer interaction or π-complex between the nitrogen lone pair and the aromatic ring in the most

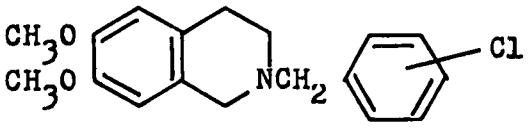
favored conformer (6a). This is in accord with electronic interactions but not with a steric effect.



6a 6b

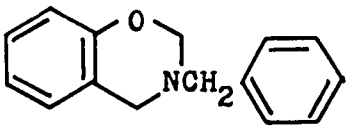
Molecular structures can be designed which contain an effective electron-donor site in one part of the molecule while in another part of the same molecule a potential electron-acceptor site exists. In the absence of a conjugated pathway between these two sites, interaction between them may still occur if the molecule can assume a conformation so that there is a finite overlap between the highest filled orbital of the donor moiety and the lowest unfilled orbital of the acceptor moiety. Charge transfer interactions have been extensively reviewed,[14] and various reports[15] have been given of optical absorptions which have been assigned to intramolecular, across space, charge transfer transitions between a neutral electron donor and a neutral electron acceptor. These absorptions usually occur at longer wavelength. The fact that the absorption obeys Beer's law provides good evidence that they are the result of intramolecular interactions rather than head-to-tail intermolecular interactions between the donor site of one molecule and the acceptor site of another molecule.

Viel[16] observed an intramolecular charge transfer band in the fluorescence spectra of 2-(chlorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (7). For this thesis a series of 2-benzyl-1,2,3,4-tetrahydroisoquinolines was prepared to determine the structural requirements for intramolecular charge transfer to be observed in the ultraviolet (uv) absorption spectra.



7

Another series of compounds related to 7 that was studied for possible intramolecular charge transfer complex formation is the 3,4-dihydro-1,3,2H-benzoxazines (8).



8

Compounds of type 8 were first synthesized by Burke[17] and later studied extensively for their potential anti-cancer properties by Kuehne.[18] This series was of interest since it possesses hetero atoms which are in a 1,3 relationship. Conformations in which unshared electron pairs on non-adjacent atoms are parallel (Figure 1) are highly disfavored because of dipole-dipole repulsions. This phenomenon has been termed

the "rabbit-ear effect".[19g] The effect should add stability to the conformation with the nitrogen substituent axial and perhaps enhance charge transfer interactions in 8.

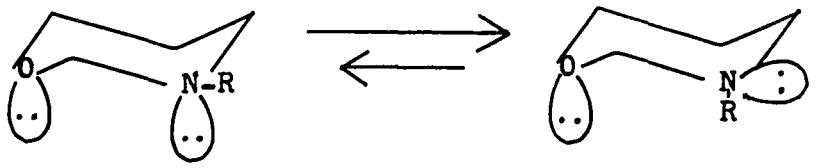


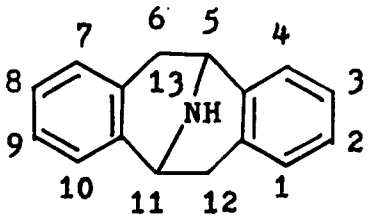
Figure 1. Rabbit-Ear Effect.

The last system that was studied in this thesis is related to an alkaloid, pavine (9). When the unripe seed capsule of the opium poppy, Papaver somniferum, is cut, a viscous liquid is exuded. After the exudate dries and darkens on exposure to air, a hard but still partly sticky mass is obtained. This is the crude opium which has been used for many centuries by some for medicinal purposes and by others to smoke in their pipes.[20] The pharmacologically active constituents of opium have been employed in medicine for hundreds of years as a mixture in the form of a highly colored tincture or as the purified component morphine alkaloids. For this reason there has been tremendous progress in the investigation of the alkaloids of the plant family, Papaveraceae. This family consists of about 700 species which are classified in approximately fifty genera.[21] Table I lists the naturally occurring pavine derivatives.

Goldschmiedt[22] first reported the synthesis of pavine by the reduction of papaverine (11) with tin and

TABLE I

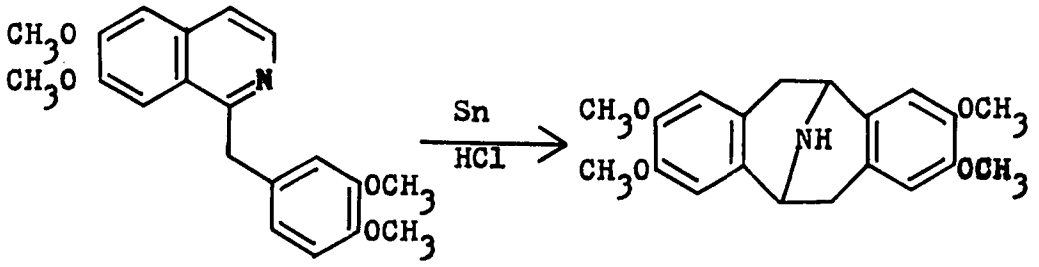
Naturally Occurring Pavine Derivatives



10

Compound	Substituent						Trivial Name
	2	3	7	8	9	13	
10a	OCH_3	OCH_3	H	OCH_3	OCH_3	CH_3	Argemonine
10b	OH	OCH_3	H	OCH_3	OCH_3	CH_3	Norargemonine
10c	OCH_3	OH	H	OCH_3	OCH_3	CH_3	Isonorargemonine
10d	OH	OH	H	OCH_3	OCH_3	CH_3	Bisnorargemonine
10e	2 OH and 2 OCH_3					CH_3	Rotundine
10f	$O\text{-}CH_2\text{-}O$		H	$O\text{-}CH_2\text{-}O$		CH_3	Eschscholtzine
10g	$O\text{-}CH_2\text{-}O$		H	$O\text{-}CH_2\text{-}O$		$(CH_3)_2$	Californidine
10h	$O\text{-}CH_2\text{-}O$		H	OCH_3	OCH_3	CH_3	Eschscholtzidine
10i	$O\text{-}CH_2\text{-}O$		H	OCH_3	OH	CH_3	Caryachine
10j	OCH_3	OH	OH	OCH_3	H	CH_3	Munitagine
10k	3 OCH_3 and 1 OH				H	CH_3	Platycerine
10l	OCH_3	OCH_3	OCH_3	OCH_3	H	CH_3	O-Methylplatycerine

hydrochloric acid, although the structure of 9 was not established at that time. Schopf[23] suggested structure 9 for pavine and Battersby and Binks[24] confirmed the structure by

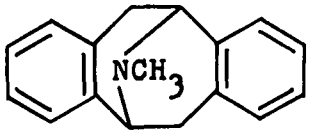


11 9

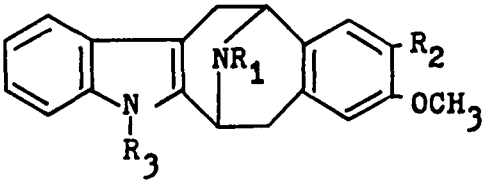
synthesis and degradation. It was then shown[25,26] that argemonine (10a) had the structure N-methylpavine. This was of special interest since argemonine was the first natural representative of a structural class which had been known previously only as an artifact.

Shavel[27] has defined a "missing alkaloid system" as a ring system, considered derivable through biogenetic processes, which has not as yet been observed in natural products. Thus, N-methylpavine could have been considered to be a representative of a "missing alkaloid system" when it was first synthesized.

Other examples of this ring system that have been synthesized to date are the parent compound (12) synthesized by Dyke,[28] and the indolopavine derivatives (13) synthesized by Shavel.[27,29] Pavine alkaloids have been shown to be active antitussive,[30] antifungal,[29] and CNS[29] agents.



12



13

It can be readily seen from Table I that extensions of the "argemonine" nomenclature quickly become cumbersome. Soine[31] has suggested that it is appropriate to introduce a new type of nomenclature for this ring system. Accordingly, it was proposed that the term "pavinane" with the numbering indicated in 10 be adopted for the tetracyclic ring system characteristic of these alkaloids.

Syntheses of pavinanes by acid catalyzed cyclizations of 1-benzyl-1,2-dihydroisoquinolines using the classical reaction conditions[24] are highly unpredictable. Many studies of this reaction have shown that in the presence of acids 1,2-dihydroisoquinolines may undergo disproportionation, polymerization, and/or rearrangement to yield 3-benzyl-3,4-dihydroisoquinolinium compounds, which then undergo disproportionation (Figure 2).[32] This type of disproportionation reaction has been shown to be a bimolecular process, and the rearrangement of 1-benzyl-1,2-dihydroisoquinolines to the 3-benzyl derivative has recently also been shown to be bimolecular.[33] The cyclization of a 1-benzyl-1,2-dihydroisoquinoline to a

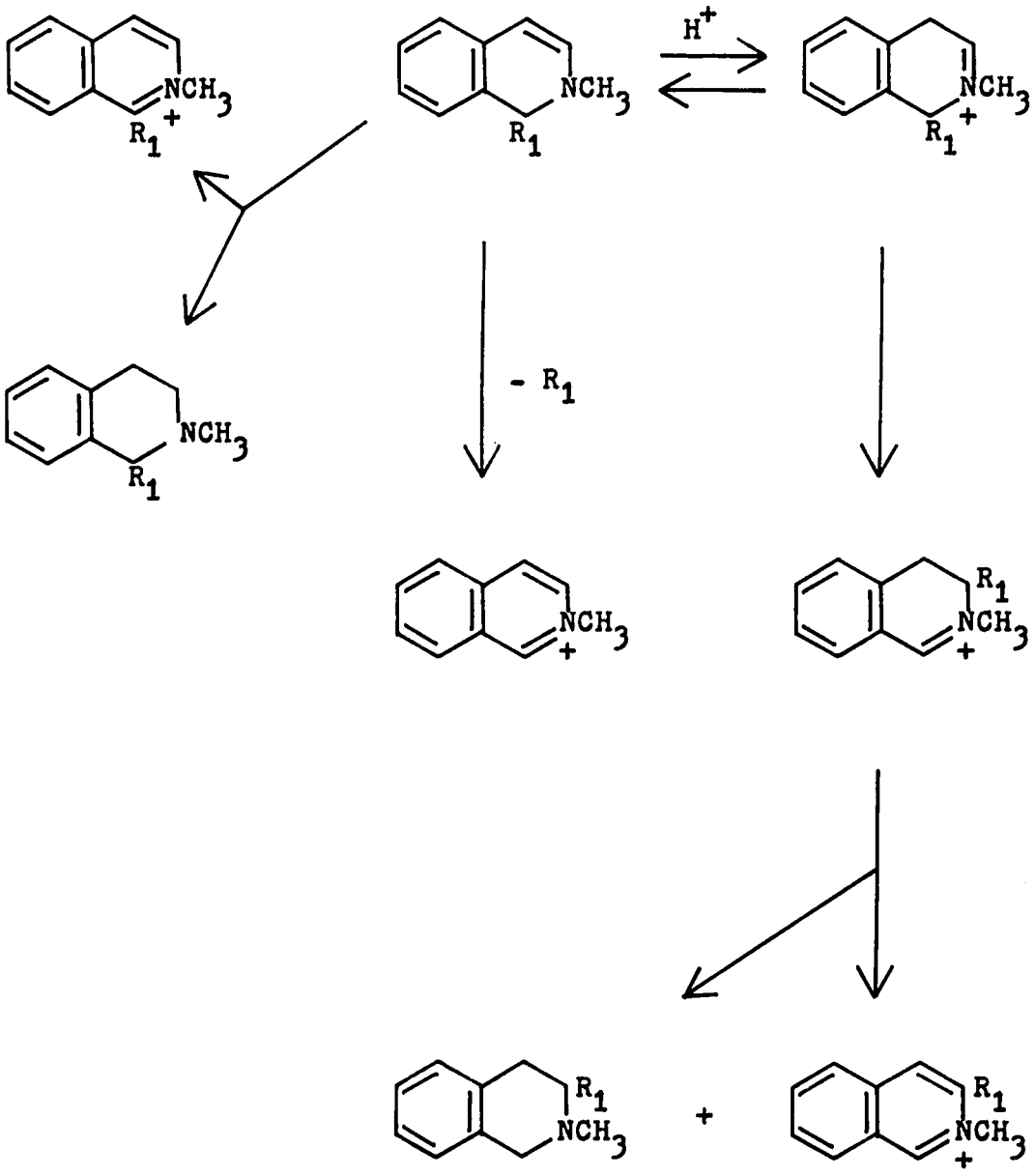


Figure 2. Acid Catalyzed Reactions of 1,2-Dihydroisoquinolines.

pavinane must be unimolecular and thus the reaction pathway favored by high dilution.

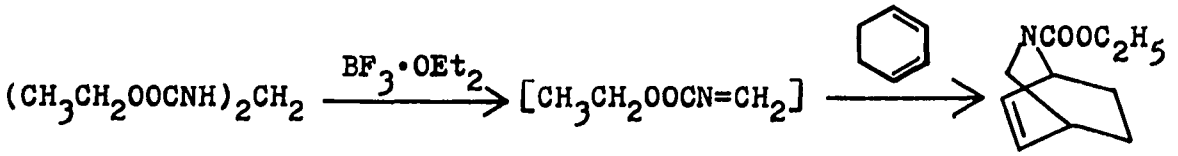
This thesis will discuss the successful syntheses of the three systems previously mentioned and a number of other systems proposed but not prepared. The consequences of intramolecular charge transfer interactions on inversion about nitrogen was investigated in these systems and the conclusions will be given.

RESULTS AND DISCUSSION

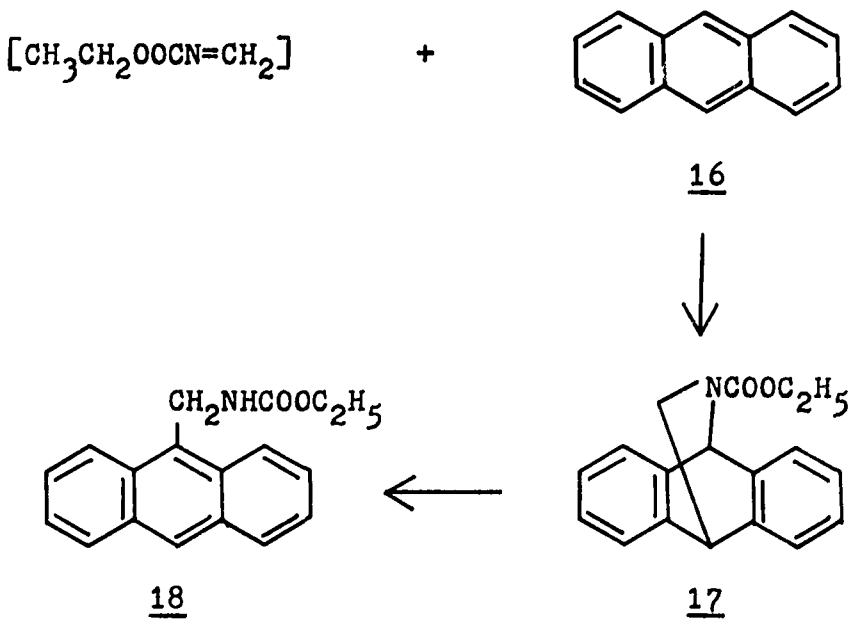
The syntheses of several nitrogen heterocyclic systems were attempted for this thesis. The reasons for the unsuccessful synthetic attempts are discussed. For the systems where synthetic attempts were successful, the syntheses and stereochemical consequences of nitrogen inversion are discussed.

Attempted Synthesis of the 10,9-(Iminomethano)anthracene Ring System

There are a large variety of ring systems which would be potentially useful in the study of intramolecular charge transfer effects on nitrogen inversion. Cava[34] reported that the Diels-Alder addition of 1,3-cyclohexadiene to methyleneurethane (generated in situ) yielded 2-ethoxycarbonyl-2-azabicyclo[2.2.2]oct-5-ene (15). Since anthracene has been shown to act as a diene in the Diels-Alder reactions,[35] the reaction with methyleneurethane as the dienophile was attempted as a possible synthesis of 10,9-(iminomethano)anthracene derivative (17).



14 15



When this reaction was carried out using benzene as solvent, only anthracene was isolated. When toluene was used as solvent a residue was isolated in 75% yield, which, after purification by chromatography on silica gel, showed spectral properties which corresponded to ethyl-9-anthracenocarbamate (18). A Friedel-Crafts type reaction could produce 18 since a Lewis acid, BF_3, is present, or 18 could arise by ring opening of 17 to give the stable aromatic nucleus. 9,10-Dimethoxyanthracene (19) was prepared[36] in order to prevent a Friedel-Crafts reaction from taking place at the 9 or 10 position on the anthracene ring. However, only starting material was isolated from the addition of methyleneurethane to 19 even when xylene was used as solvent.

While this work was in progress, the report by Wilkins[37] of a previous attempt of this synthesis of 17 was found. He also isolated 18 as well as a 9,10-dialkylated

anthracene derivative. The dialkylated derivative would undergo facile Diels-Alder reaction with maleic anhydride but would not undergo further reaction with methyleneurethane even at 140°. Wilkins' results indicate that the reaction does not involve a concerted addition of an imine to the anthracene. The synthesis of this ring system was not pursued further.

Synthesis and Spectral Studies of 2-Benzyl-1,2,3,4-tetrahydroisoquinolines.

A series of 2-benzyl-1,2,3,4-tetrahydroisoquinolines was synthesized by the routes outlined in Figure 3. The isoquinoline and a benzyl halide underwent reaction to give a salt, and this salt was reduced with sodium borohydride in ethanol to yield the tetrahydroisoquinoline. The reduction of nitrogen heterocycles with complex metal hydrides has been reviewed by Lyle and Andersen.[38]

When 6,7-dimethoxy-3,4-dihydroisoquinoline (24) was mixed with 2,4-dinitrobenzyl bromide (23) in tetrahydrofuran, the expected salt did not precipitate but instead the reaction mixture darkened and only tars could be isolated. A disproportionation or oxidation-reduction reaction could have occurred between a nitro group and the dihydroisoquinoline, and this reaction would result in decomposition of the reaction mixture. This complication was avoided by converting the isoquinoline to the tetrahydro secondary amine by reduction over platinum in an acidic solution. An anion of the secondary amine was formed using sodium hydride and then the

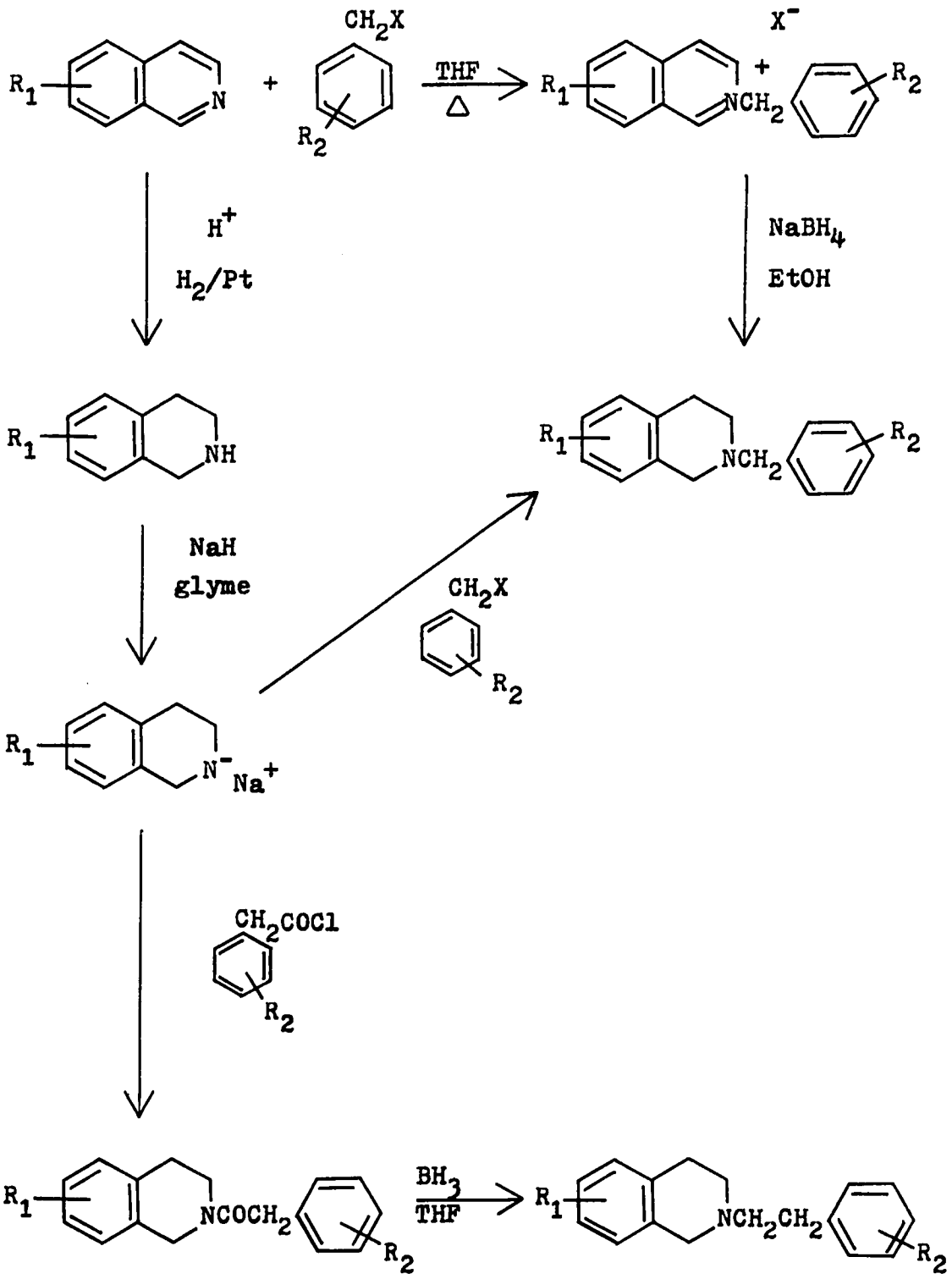
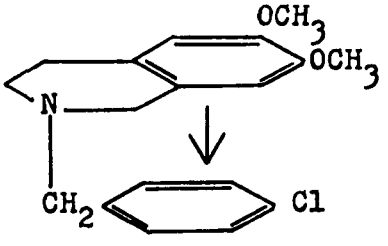


Figure 3. The Synthesis of 2-Benzyl-1,2,3,4-tetrahydroisoquinolines.

anion was mixed with the benzyl halide to yield the benzyl-tetrahydroisoquinoline.

The 2-(β-phenethyl)tetrahydroisoquinolines were most conveniently prepared by performing a Schotten-Baumann reaction with the tetrahydroisoquinoline and a phenylacetyl chloride. The resulting amide could be reduced with a solution of dibroane in tetrahydrofuran.[39] Table II lists the tetrahydroisoquinolines that were prepared.

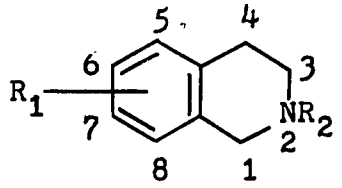
Intramolecular charge transfer interactions, when observable, can be detected as an extra absorption in addition to that of a suitable reference in the uv or visible spectrum. Viel[16] observed an intramolecular charge transfer band for 7 in the fluorescence spectrum. This extra absorption band is due to electron transfer from an electron rich aromatic system to an electron deficient aromatic system. Ultraviolet adsorption studies at a concentration of 10^{-4} M in methanol were performed on the compounds in Table II and on their proton salts.



7

TABLE II

Tetrahydroisoquinolines



Compound	R_1	R_2
37	H	H
38	H	CH_3
39	H	benzyl
40	H	2',6'-dichlorobenzyl
41	H	4'-nitrobenzyl
42	H	2',4'-dinitrobenzyl
43	H	4'-methoxybenzyl
44	H	3',4'-dimethoxybenzyl
45	H	β-(4'-nitrophenyl)ethyl
46	6,7-dimethoxy	H
47	6,7-dimethoxy	CH_3
48	6,7-dimethoxy	benzyl
49	6,7-dimethoxy	2',6'-dichlorobenzyl
50	6,7-dimethoxy	4'-nitrobenzyl
51	6,7-dimethoxy	2',4'-dinitrobenzyl
52	6,7-dimethoxy	β-(4'-nitrophenyl)ethyl
53	5-nitro	CH_3
54	5-nitro	benzyl
55	5-nitro	4'-methoxybenzyl
56	5-nitro	3',4'-dimethoxybenzyl

Compounds 37 to 45 were selected as suitable references since there is no substitution in the isoquinoline portion of the molecules and thus no charge transfer would be expected. In addition, the uv spectrum of each portion of the molecule was recorded. The algebraic sum of these spectra were compared with that of the parent compound. For example, the uv spectrum of 2-(4'-nitrobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (50) was recorded. Compound 41 would be used as a reference as well as the algebraic sum of the spectra of 47 and p-nitrotoluene. The uv spectrum of a 1:1 molar solution of known concentration of p-nitrotoluene and 47 was also determined. Any extra absorption band that occurred in the spectrum of 50 at 10^{-4}M could be attributed to intramolecular charge transfer. Intermolecular interactions are not observable at concentrations less than 10^{-2}M.[14]

Intramolecular charge transfer could be observed in the uv spectrum only for 2-(2',6'-dichlorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (49). An extra absorption band appeared at 370 nm (ϵ100) which did not occur in any of the reference spectra (Figure 4).

Since many of the tetrahydroisoquinolines prepared were oils, uv absorption studies were performed on their proton salts. The uv spectra of the bases and proton salts of all solid tetrahydroisoquinolines were virtually identical. The proton salts could be prepared in analytical purity and were easily manipulated. The uv spectrum of the hydrochloride of 49 also showed an intramolecular charge transfer band at 370 nm.

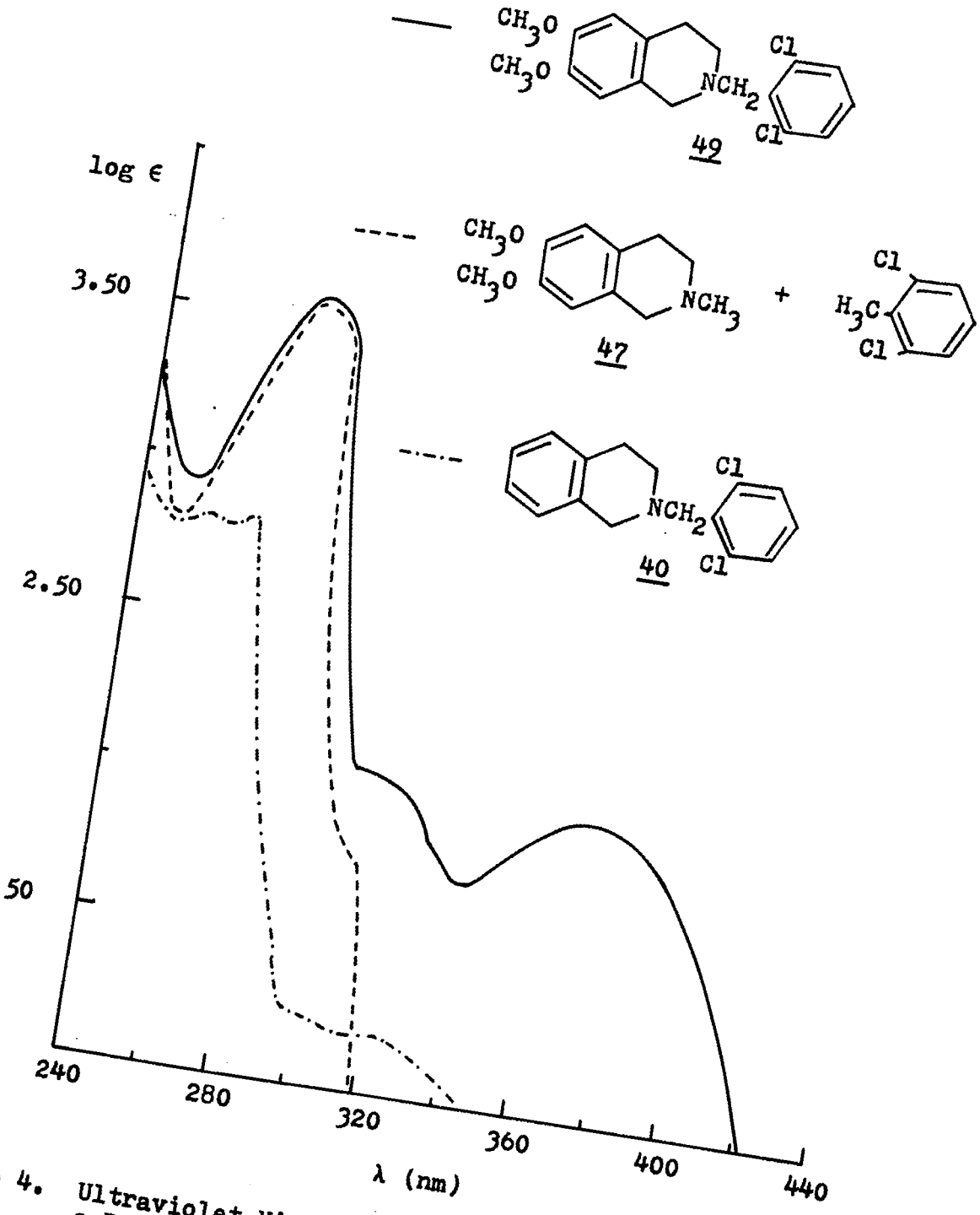


Figure 4. Ultraviolet-Visible Absorption Spectra of 40, 49, and a Reference of a Combination of 47 and 2,6-dichloro-toluene.

While most of the tetrahydroisoquinolines prepared were white or pale yellow in color, 42 was isolated as orange needles. Compound 51 is a yellow-brown solid which is not stable as the base. Both 42 and 51 contain the 2,4-dinitrobenzyl substituent on the nitrogen. The anomalous behavior of these compounds is attributed to the fact that they have the possibility of forming Meisenheimer type complexes[40] either internally or as dimers (Figure 5). Formation of Meisenheimer type complexes is prevented when the nitrogen is protonated. The proton salts of both 42 and 51 are white.

Nitro substituents in the benzyl portion of the molecule showed only a hint of extra absorption (Figure 6). Increasing the chain length to the phenethyl series did not increase the amount of any interactions (Figure 7). Compounds containing a nitro substituent in the 5-position of the isoquinoline ring did not show any extra absorptions in their uv spectra (Figure 8).

The absence of any extra absorptions in the uv spectrum could indicate that no intramolecular charge transfer was occurring or that the charge transfer band was obscured by other transitions. If the 2-benzyl-tetrahydroisoquinolines occur to any appreciable degree in a folded conformation with the aromatic rings face-to-face, intramolecular (de)shielding effects in the nmr spectra should be observed. It has been shown[15k] for a series of benzylphenylsulfones that the shifts of the aromatic protons in the nmr spectra can be correlated with an appearance of an intramolecular charge transfer band in the uv spectra. Table III lists the chemical shifts of

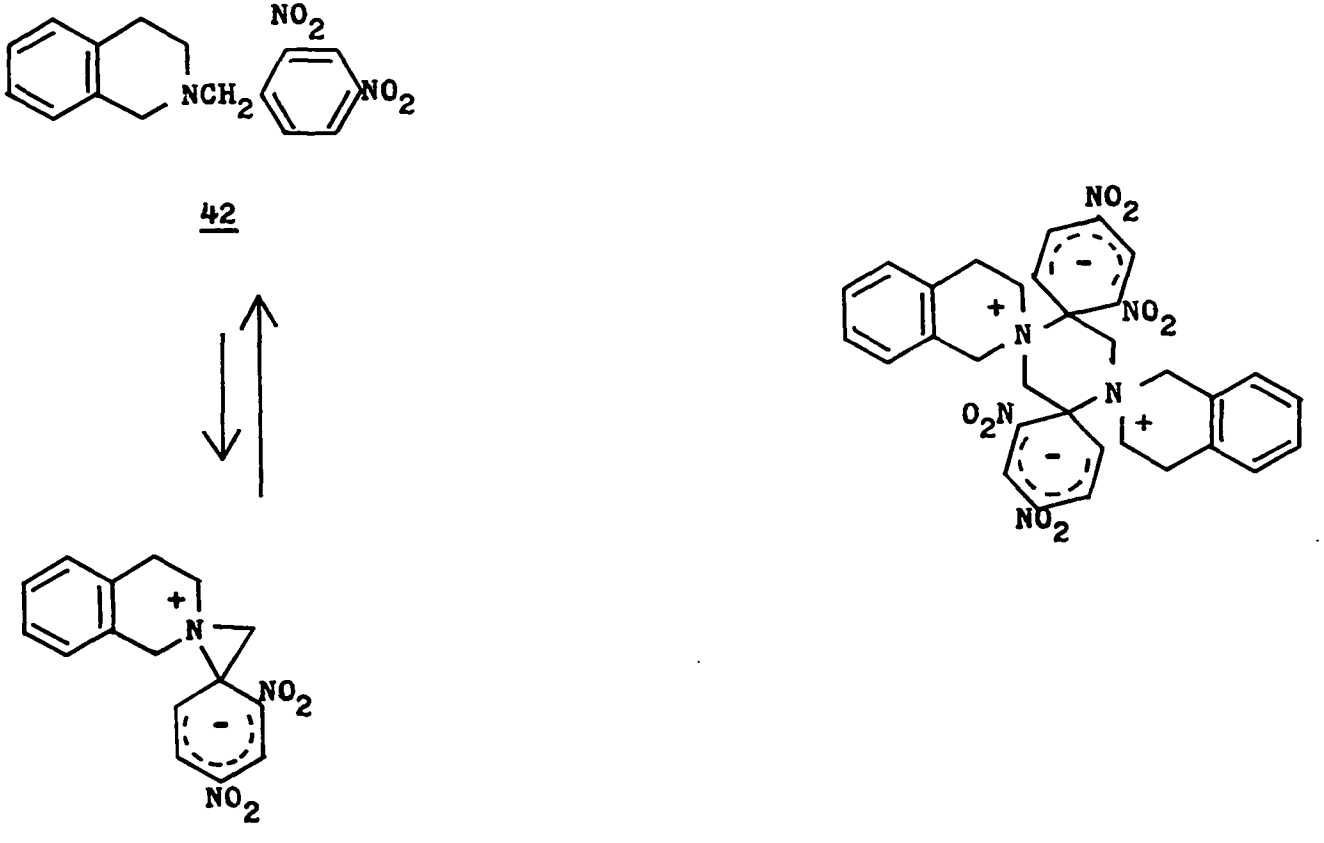


Figure 5. Internal Meisenheimer Complexes of 2-(2',4'-Dinitrobenzyl)-1,2,3,4-tetrahydroisoquinoline.

10^{-4} M in methanol

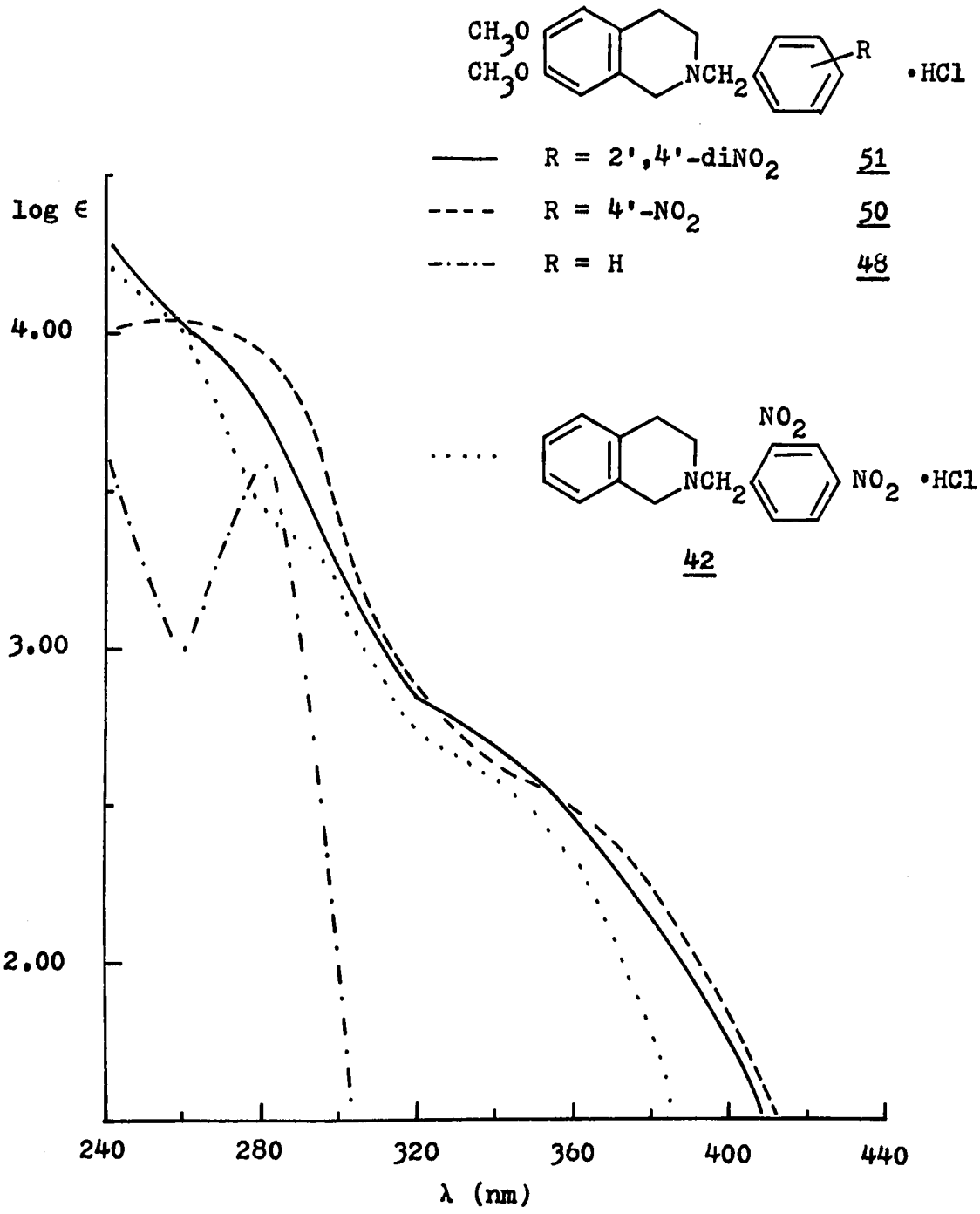


Figure 6. Ultraviolet-Visible Absorption Spectra of the Proton Salts of 42, 48, 50, and 51.

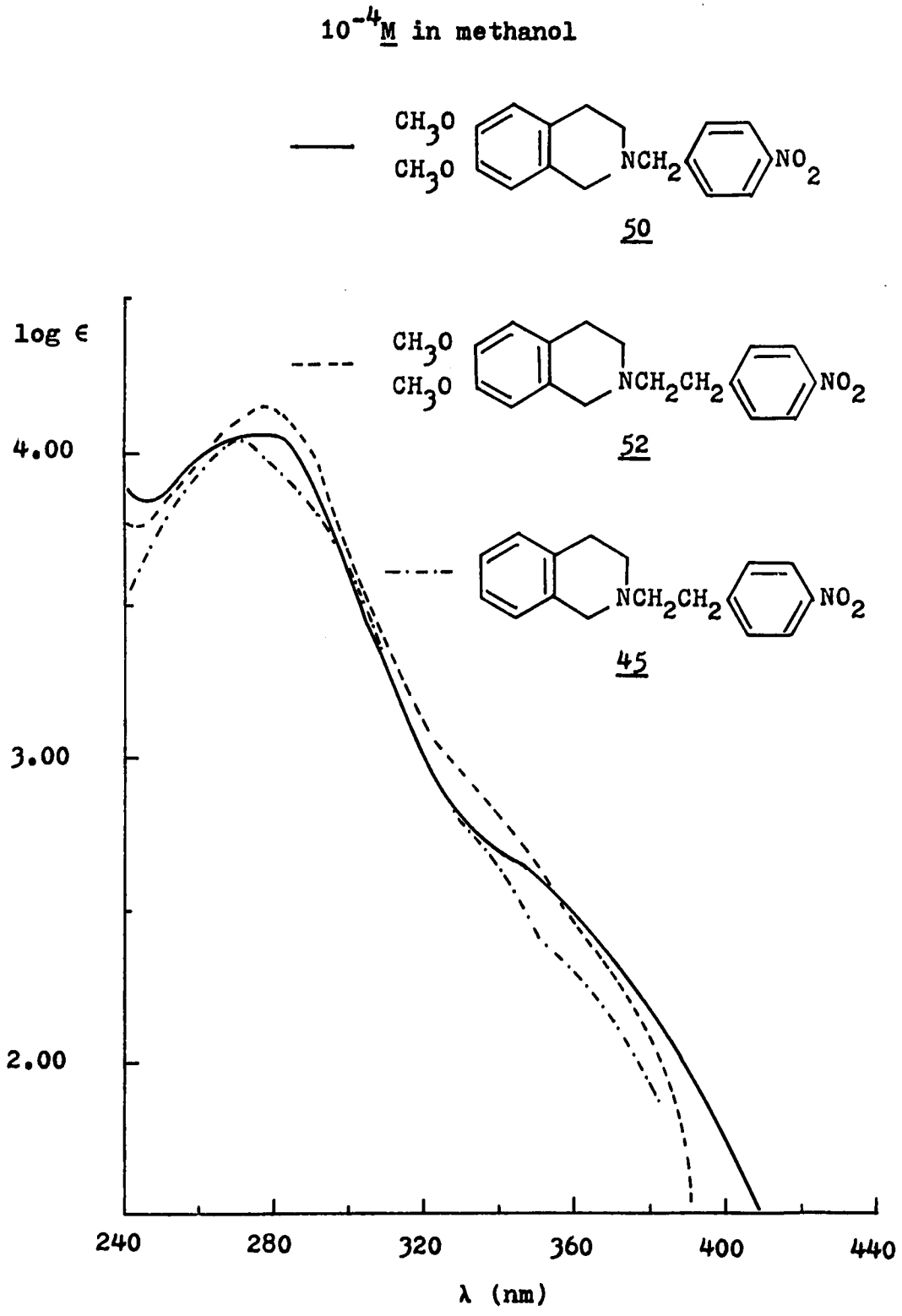


Figure 7. Ultraviolet-Visible Absorption Spectra of 45, 50, and 52.

10^{-4} M in methanol

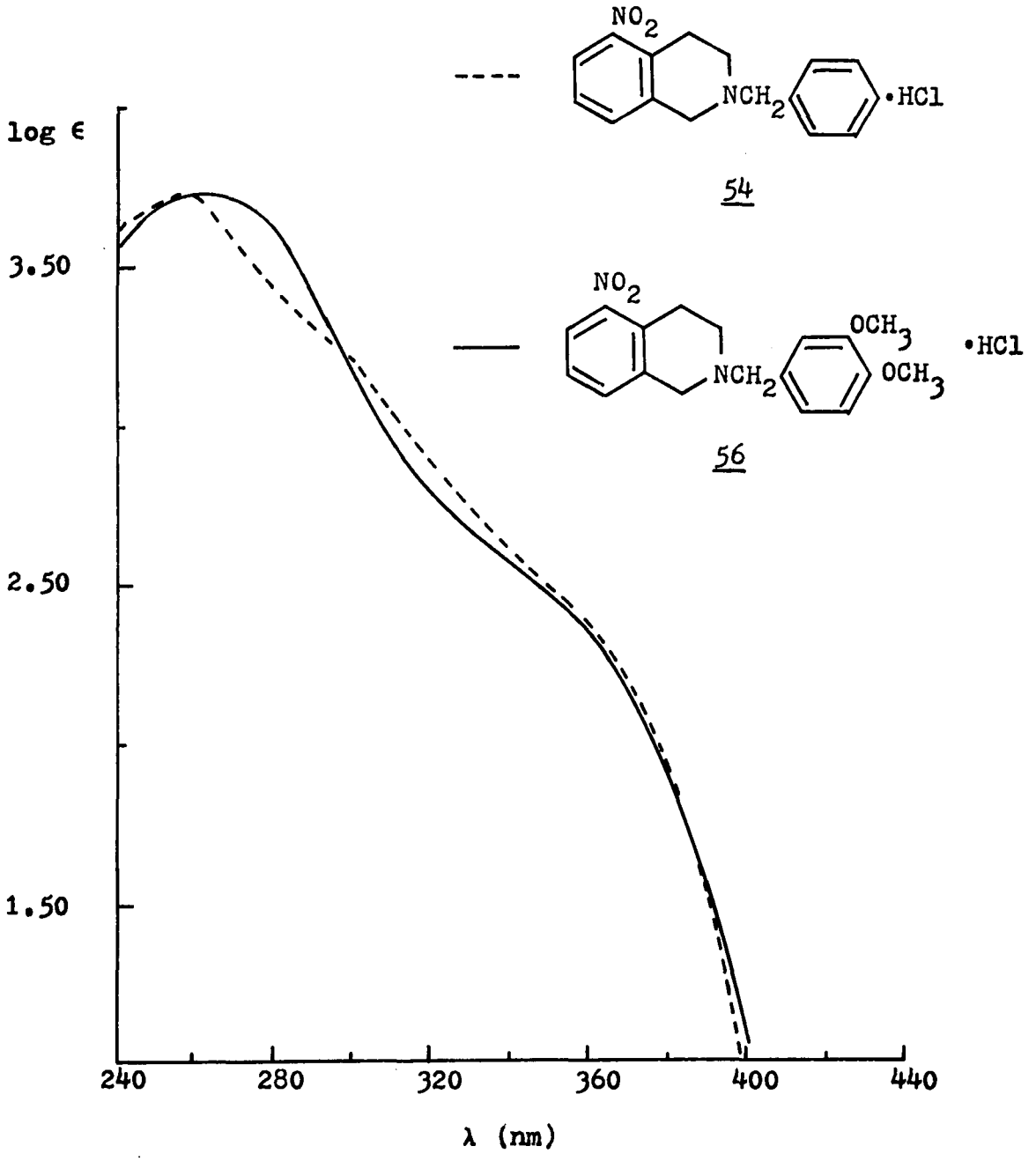
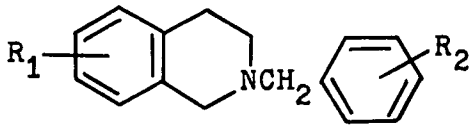


Figure 8. Ultraviolet-Visible Absorption Spectra of the Proton Salts of 54 and 56.

the aromatic protons for compound 49 which had a charge transfer adsorption band in its uv spectrum. Compared with reference compounds 40 and 48, the aromatic protons of 49 are shifted only slightly compared with values of ca. 0.15-0.40 ppm obtained for the benzylphenylsulfones.[15k] No conclusive evidence for a face-to-face interaction can be obtained from these data.

TABLE III

Chemical Shifts of Aromatic Protons



Compound	δ Isoquinoline H	δ Benzyl H
40 R_1=H, R_2=2',6'-diCl	--	7.24
48 R_1=6,7-diOCH_3, R_2=H	6.58, 6.46	--
49 R_1=6,7-diOCH_3, R_2=2',6'-diCl	6.53, 6.47	7.20

The ring methylene and benzyl protons in the benzyltetrahydroisoquinolines are diastereotopic.[41] As nitrogen inversion slows, the nmr signal for these protons should change from a sharp singlet to an AB quartet. Low temperature nmr spectra of 41, 48, 49 and 50 were recorded in methylene chloride to -90°. No change in any of the signals for any of the compounds was observed.

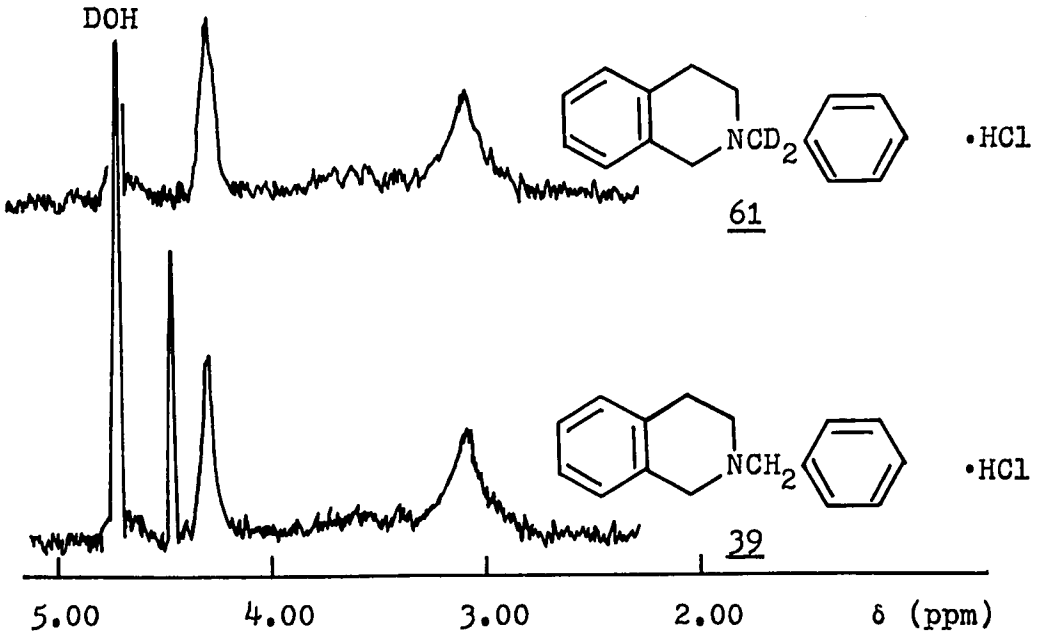
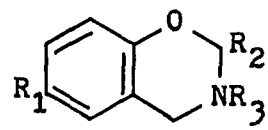


Figure 9. The NMR Spectra of the Proton Salts of 39 and 61.

Protonation of the nitrogen slows down inversion.[9] The nmr spectrum of the hydrochloride of 39 shown in Figure 9 indicates that inversion about nitrogen has been slowed. One of the two methylene signals has been considerably broadened. Labeling the benzyl group with deuterium shows that the broader signal arises from the more constrained, ring-methylene group. A double resonance experiment showed that this broadening was not due to long range coupling with the protons in the 3 or 4 position of the tetrahydroisoquinoline ring or with the proton in the 8 position. Upon addition of acid to a D_2O solution of 39, the methylene peak broadens even further and begins to split into a multiplet; however, the salt precipitates before the signal splits sufficiently enough to obtain coupling constants. No suitable solvent could be found to keep the salt in solution at low temperature or low pH.

TABLE IV

3,4-Dihydro-1,3,2H-benzoxazines



Compound	R_1	R_2	R_3	% Yield
69	OCH_3	H	CH_3	44
70	OCH_3	H	CH_2Ph	41
71	OCH_3	H	CH_2-4'-NO_2Ph	39
72	OCH_3	H	CH_2CH_2Ph	63
73	OCH_3	H	CH_2CH_2-4'-NO_2Ph	65
74	OCH_3	H	CH_2-2',6'-diClPh	36
75	CH_3	H	CH_2Ph	54
76	CH_3	4'-ClPh	CH_2Ph	66

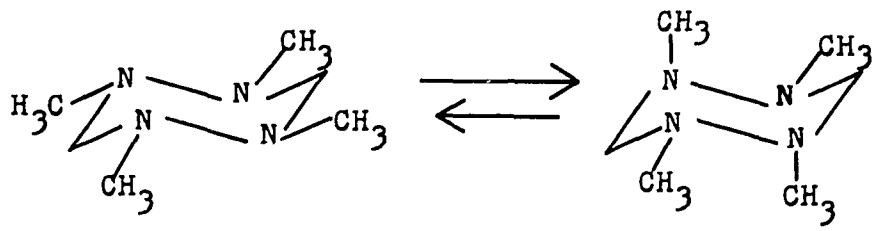
Synthesis and Spectral Studies of 3-Benzyl-3,4-Dihydro-1,3,2H-benzoxazines.

A series of 3-benzyl-3,4-dihydro-1,3,2H-benzoxazines (8) was synthesized by the condensation of a phenol, a primary amine and two moles of formaldehyde, a procedure first utilized by Burke.[17] Table IV lists the compounds that were prepared. The condensation of p-chlorobenzaldehyde and 2-benzylaminomethyl-4-methylphenol (77) with removal of water yielded 76. The acid catalyzed hydrolysis[17] of 75 gave 77.

The uv spectra at 10^{-4}M in methanol of compounds 69 to 74 showed no extra absorptions above those of reference

samples. No intramolecular charge transfer interactions could be observed for this system.

The benzoxazine ring system was studied in the hope that the 1,3-dipole-dipole interaction, the "rabbit-ear effect",[19] would enhance any charge transfer interactions. Roberts[19b] has found for tetramethylhexahydrotetrazine (92) that two of the methyl substituents prefer to be axial. He attributes this preference to unfavorable nitrogen lone pair-lone pair interactions in 92a.



92a 92b

Low temperature nmr spectra of 70 and 71 were recorded in methylene chloride to -90°. No change in any of the signals for either compound was observed.

It was observed that when a 3,4-dihydro-1,3,2H-benzoxazine was treated with borane and the adduct was heated, a rearrangement occurred. When 81 was recrystallized from cyclohexane-benzene, a singlet at 2.51 ppm appeared in the nmr spectrum. This signal is in the region corresponding to a N-Me resonance. The signal associated with the methylene group bonded to the N and O had also disappeared. This indicated that ring opening and reduction had occurred. The infrared spectrum showed an absence of OH stretching

adsorption but strong B-H adsorption at 2400 cm^{-1}. Structure 86 was assigned to this product. Ring opened structures of type 93 were eliminated since the ring methylene group bonded to the N and substituted aromatic ring appeared as an AB quartet. The methylene signals in 93 should appear as singlets due to free rotation about the C-N bond and rapid inversion of nitrogen configuration.

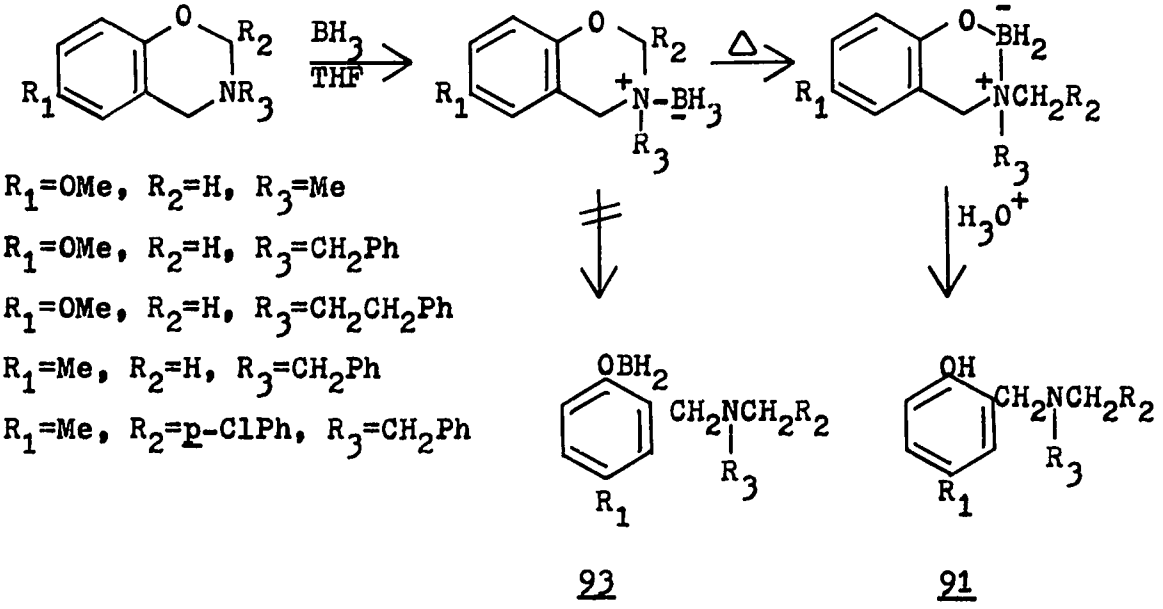
The rearranged product was shown by the spectral data to belong to a ring system known as [4H]-1-oxa-3-azonia-2-boratanaphthalenes (OABN).[96] The name describes the state of reduction for compounds 85 to 88 obtained from the rearrangement of the amine boranes 80 to 83. Table V lists the compounds prepared.

The 1,3,2H-benzoxazaborine ring system has previously been synthesized by condensation of phenylboronic acid with o-hydroxybenzylamine,[42] and by thermal cyclization of the adduct of borane and salicylideneaniline.[43] Borane was added to a tetrahydrofuran solution of the benzoxazine and after 30 min the solvent was evaporated to give the adducts (80 to 84) as white solids. Heating these solids neat at 180° for 20 min yielded the rearranged OABN (85 to 88). Treatment of 86 with aqueous hydrochloric acid gave 2-(benzylmethylaminomethyl)-4-methoxyphenol (91). The nmr spectral data for the amine boranes and the OABN derivatives are listed in Table VI. The methyl iodide (78) and benzyl bromide (79) salts of 75 were prepared for an nmr comparison with the OABNs.

The signals for the ring methylene groups in the adducts (80 to 84) are all AB quartets due to the quaternary,

TABLE V

[4H]-1-Oxa-3-azonia-2-boratanaphthalenes (OABN)



69 R_1=OMe, R_2=H, R_3=Me

70 R_1=OMe, R_2=H, R_3=CH_2Ph

72 R_1=OMe, R_2=H, R_3=CH_2CH_2Ph

75 R_1=Me, R_2=H, R_3=CH_2Ph

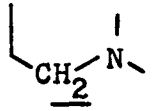
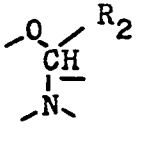
76 R_1=Me, R_2=p-ClPh, R_3=CH_2Ph

93 91

Benzoxazine	BH_3•Adduct	OABN (% yield)
69	80	85 (68)
70	81	86 (53)
72	82	87 (78)
75	83	88 (54)
76	84	89 (--)

TABLE VI

NMR Spectral Data for Borane Adducts of
Benzoxazines and Oxazoniaboratanaphthalenes

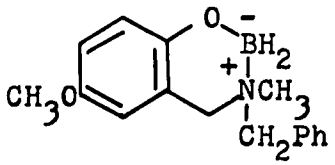
Compound	R_1		R_3		NCH_3
80	(s) 3.78	(dd) 4.12* J=18, Δν=52	(s) 2.70	(dd) 4.60 J=10, Δν=10	--
82	(s) 3.81	(dd) 4.12 J=17, Δν=39	(m) 3.08	(dd) 4.68 J=10, Δν=32	--
83	(s) 2.24	(dd) 4.02 J=17, Δν=22	(s) 3.90	(dd) 4.50 J=10, Δν=7	--
84	(s) 2.24	(dd) 4.04 J=18, Δν=**	(s) 4.00	(m) 6.16	--
85	(s) 3.76	(s) 3.96	(s) 2.68	--	(s) 2.68
86	(s) 3.80	(dd) 4.04 J=14, Δν=19.5	(dd) 3.84 J=14, Δν=15.6	--	(s) 2.52
87	(s) 3.73	(dd) 3.98 J=14.5, Δν=8.9	(m) 3.08	--	(s) 2.64
88	(s) 2.28	(dd) 4.04 J=13, Δν=17.7	(dd) 3.80 J=14.5, Δν=16.4	--	(s) 2.52
78	(s) 2.24	(dd) 4.84 J=15.5, Δν=31.4	(s) 3.82	(dd) 5.40 J=8.5, Δν=11	(s) 3.08
79	(s) 2.32	(s) 5.16	(s) 5.36	(s) 5.44	--

* δ in ppm, J and Δν in Hz

** a portion of the signal was obscured by THF

asymmetric nitrogen. The N-benzyl signal, however, appears as a singlet. In 80 and 84, a long range 1,3-coupling (J = 2.5 Hz) was observed between one hydrogen of each methylene group. The signal farthest downfield for the Ar-CH-N and the signal farthest upfield for the O-CH-N were each split into a doublet of doublets. Irradiation of the upfield signal relaxed the downfield signal to a doublet.

In the benzoxazaborines, 86 and 88, both the ring methylenes and the N-benzyl signals appear as AB quartets. However, the N-benzyl signal in 78 is a singlet, since the N is bonded to two ring methylene groups while in 86 the N is bonded to one ring methylene group and to a B atom. In each case the N-benzyl protons are diastereotopic. However, in 78 the magnetic fields associated with each ring methylene are not sufficiently different to observably influence the N-benzyl protons. The magnetic fields associated with the ring methylene and the boron atom are sufficiently different in 86 to cause the N-benzyl signal to appear as an AB quartet.



86

78

Anomalous behavior was observed when 76 was treated with diborane. A white solid (mp 196°) precipitated from the THF solution. This solid was insoluble in most aprotic, organic solvents. The infrared spectrum showed a B-H stretching adsorption, and the nmr spectrum showed signals at 6.16, 4.00 and 4.04 ppm which were indicative of the amine borane, 84. This compound was the only adduct prepared which had a substituent in the 2-position. This could account for the low solubility and high melting point. The acyclic structure 94 (Figure 10) could not be eliminated for this compound although 94 should be quite reactive and undergo reduction or polymerization readily. For these reasons 94 was considered an unlikely structure.

Mikhailov[43] has isolated a high melting, insoluble substance from the borane addition to salicylideneaniline. He suggested that this material is a trimer of 93, probably formed through donor-acceptor bonds. The amine borane, 84, is quite sterically hindered because of the bulky groups on the nitrogen and on the 2-position, and could undergo ring cleavage and reduction to give 93. On heating, 93, which now contains three large groups on the nitrogen, could undergo hydrolysis in preference to cyclization to yield 90.

When 84 was heated to 220°, the expected product of rearrangement, 89, was not observed but instead the ring opened tribenzylamine (90) was obtained. The three N-benzylic signals appeared as three singlets at 3.56, 3.58, and 3.68 ppm in the nmr spectrum and the infrared spectrum showed an OH stretching adsorption.

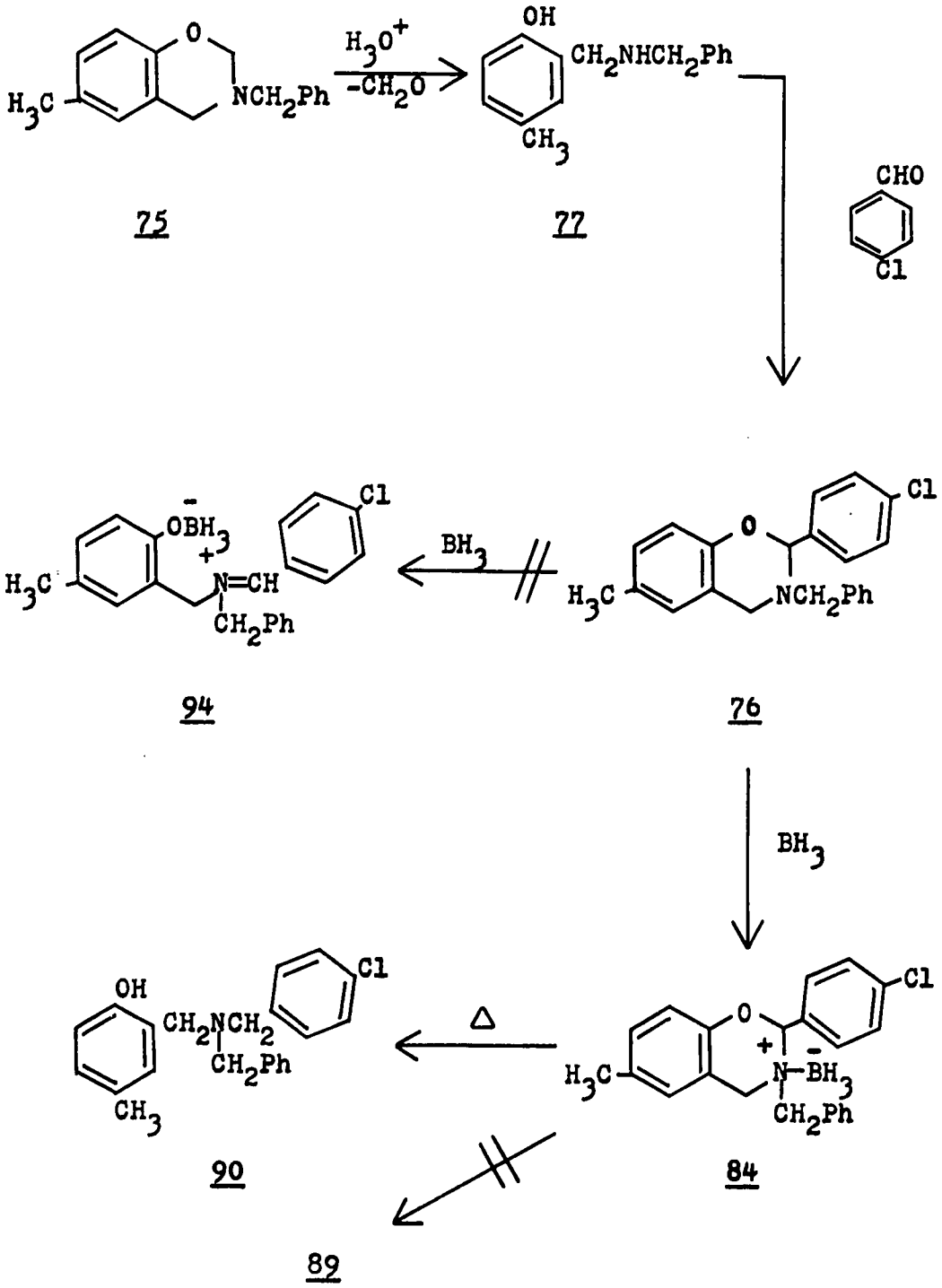
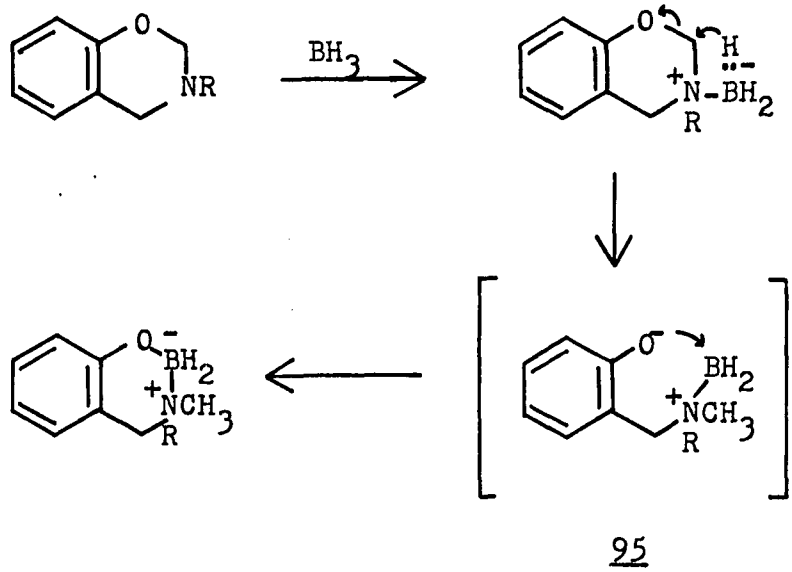


Figure 10. The Synthesis and Reactions of 3,4-Dihydro-2-p-chlorophenyl-3-benzyl-6-methyl-1,3,2H-benzoxazine.



95

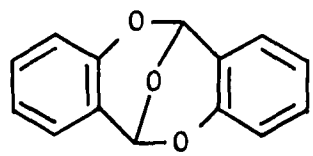
Figure 11. Possible Mechanism for Rearrangement.

Figure 11 diagrams a possible mechanism for the rearrangement. A four-centered cyclic transition state with attack of hydride on the ring methylene could give the open-chained intermediate 95, which could then cyclize to the OABN. The substituent in the 2-position of 84 could hinder hydride attack and/or cyclization and result in the formation of 90.

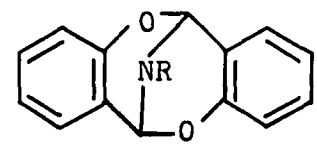
Synthetic Approaches to the 6,12-Imino-6H,12H-dibenzo[b,f]-1,5-dioxacin Ring System

Since the middle of the nineteenth century salicylaldehyde has been known to dimerize under a variety of conditions. It was not until 1922 that Adams[44] assigned the correct structure, 6,12-epoxy-6H,12H-dibenzo[b,f]-1,5-

dioxacin (98), to the dimer. The nitrogen analog (102) of disalicylaldehyde would provide an interesting system for the study of intramolecular charge transfer effects and the effect of this interaction on nitrogen inversion. The aromatic rings of 102 are electron rich because of the oxygen substituent, and if an electron deficient aryl system were attached to the nitrogen, there would be the possibility of interaction between the aromatic rings. This interaction should have an effect on the barrier to inversion of the groups about nitrogen. In addition, there would be two 1,3-dipolar interactions, reminiscent of benzoxazines, which could also influence nitrogen inversion.



98

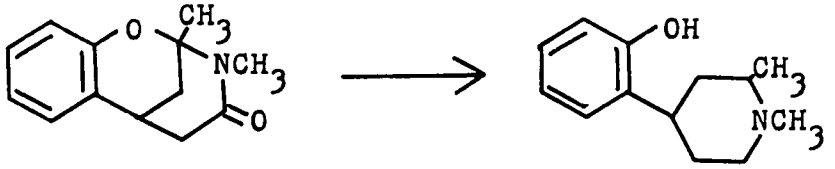


99 R=$COOC_2H_5$
100 R=$COOCH_2Ph$
101 R=COPh
102 R=H
103 R=CH_3

Merten and Muller[45] reported the first example of the 6,12-imino-6H,12H-dibenzo[b,f]-1,5-dioxacin ring system when they synthesized 99 from salicylaldehyde and ethylcarbamate using borontrifluoride•diethyl etherate as a catalyst. Derivatives of 98 are unstable to acid[44] and the urethane esters are notoriously difficult to hydrolyze in base.[34] The

synthesis of 99 was accomplished and the compound was subjected to reduction with lithium aluminum hydride in tetrahydrofuran. Only polymeric material was isolated. The carbobenzoxy analog, 100, was synthesized and subjected to hydrogenation over palladium-on-charcoal. A compound was isolated from this reaction which had physical properties and spectral data that did not correspond with the structure 102 but to the ring-opened bis-(o-hydroxybenzyl)amine (104). The attempted synthesis of 101 starting with salicylaldehyde and benzamide gave a compound (105) of as yet undetermined structure.

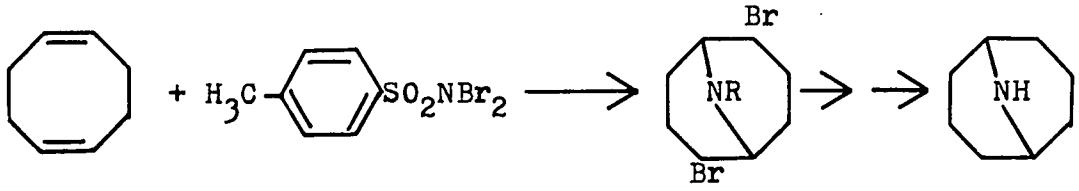
These observations are comparable to the results obtained by Razdan[46] for the 1,3-benzoxazacine ring system (106). He found that reduction of 106 with lithium aluminum hydride, aluminum hydride and diborane gave only the product of ring cleavage, 107. Since a substituent on nitrogen could not be cleaved successfully to give 102, further attempts aimed at the synthesis of 102 were suspended.



106 107

Synthetic Approaches to the Pavinane Alkaloids

Stetter and Heckel[47] have reported that 1,5-cyclooctadiene (134) and N,N-dibromo-p-toluenesulfonamide (135) underwent reaction to form the addition product (136). Thus a dibenzocyclooctatetraene system (138) should undergo reaction with a nitrene-type reagent to yield the pavinane ring system. Derivatives of 138 are not readily available but a possible synthetic route from the corresponding dibenzsuberone (139) is shown in Figure 12. Cope[48] found the dehydrobromination of compounds of type 140 with amines resulted in molecular rearrangement and the formation of 141 instead of the desired 138. Cioranescu[49] obtained similar results using acidic conditions for the elimination. This synthetic approach to the pavinane skeleton was thus abandoned.



134 135 136

The classical synthetic approach to the pavinane alkaloids utilizes the fact that 1,2-dihydroisoquinolines should exhibit enamine character[24,32] and should be susceptible to electrophilic attack at the 4-position. Particularly when the electrophile is a proton, the 1,2-dihydroisoquinoline should undergo nucleophilic attack at the 3-position (Figure 2, p 12). Using 2,3-dimethoxy-N-methylpavinane (128) as an

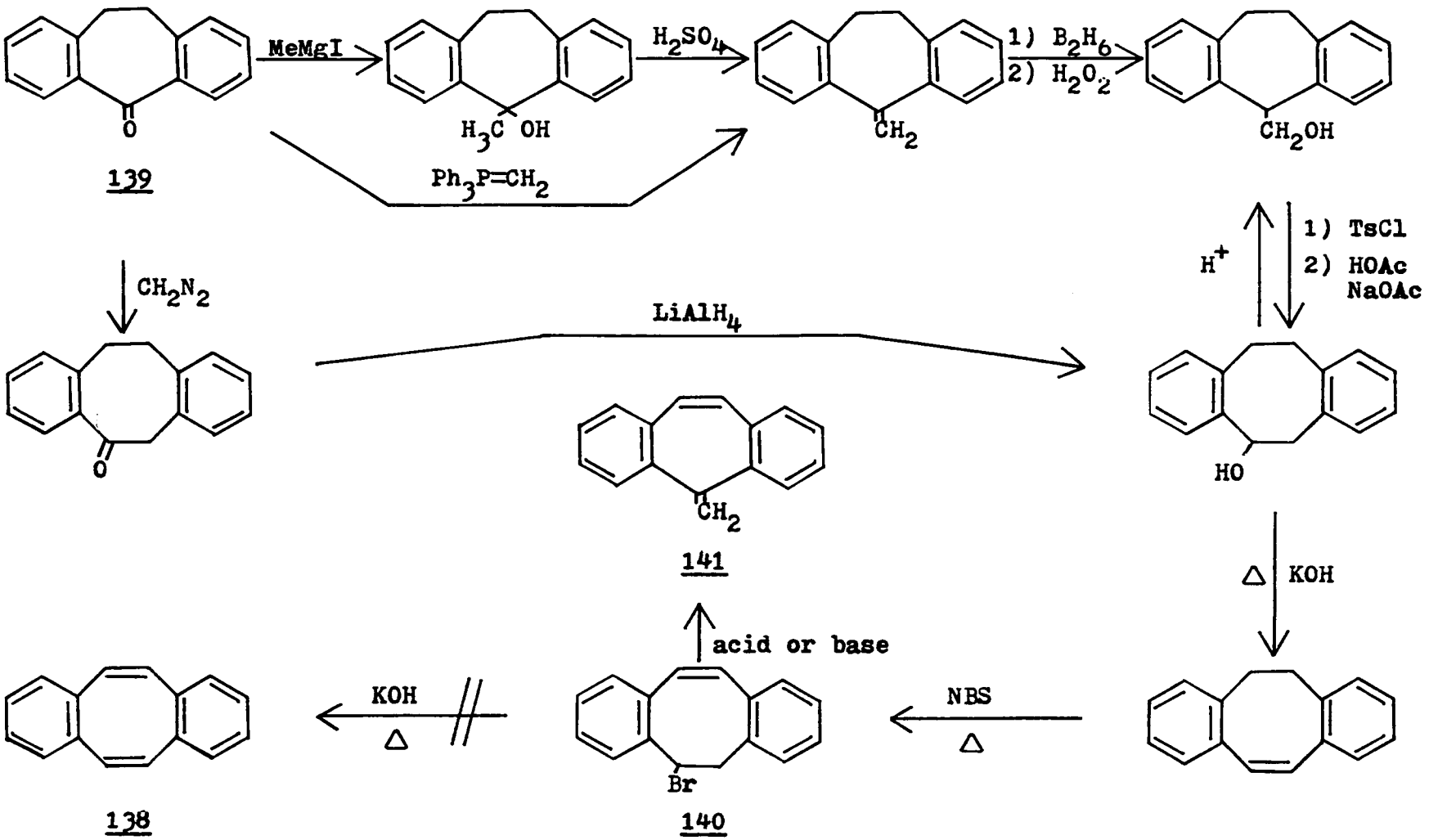


Figure 12. An Approach to the Synthesis of sym-Dibenzocyclooctatetraene.

example, this approach is outlined in Figure 13.

The chemistry of Reissert compounds has been reviewed extensively[50] and these compounds have become the intermediate of choice for the preparation of 1-substituted isoquinolines. 1-Cyano-2-benzoyl-1,2-dihydroisoquinoline (108) was prepared by the method of Popp and Blount[51] in 79% yield. The anion of the Reissert compound can be generated at room temperature with sodium hydride in dimethylformamide.[52] 3,4-Dimethoxybenzyl bromide (21) was added, and the alkylated Reissert compound was hydrolyzed with base to give 1-(3',4'-dimethoxybenzyl)isoquinoline (110). This base was converted quantitatively to the quaternary salt (112) by heating with methyl iodide.

There are at least three general methods for the reduction of isoquinolinium salts to 1,2-dihydroisoquinolines. Shavel[27] reduced the salts with lithium aluminum hydride in tetrahydrofuran by stirring the mixture at room temperature overnight. This method gave unsatisfactory results in the present work.

The reduction of 112 overnight with sodium borohydride in ethanol at room temperature gave the tetrahydro derivative, 120, in good yield. Barton,[53] however, found that sodium borohydride reduction in an aprotic solvent such as pyridine stopped at the dihydroisoquinoline. This is consistent with predictions made by Lyle and Anderson[38] based on the mechanism of reduction of isoquinolinium salts. When there is no proton available for electrophilic attack at the 4-position of the isoquinoline ring, the reduction stops at the 1,2-dihydro stage.

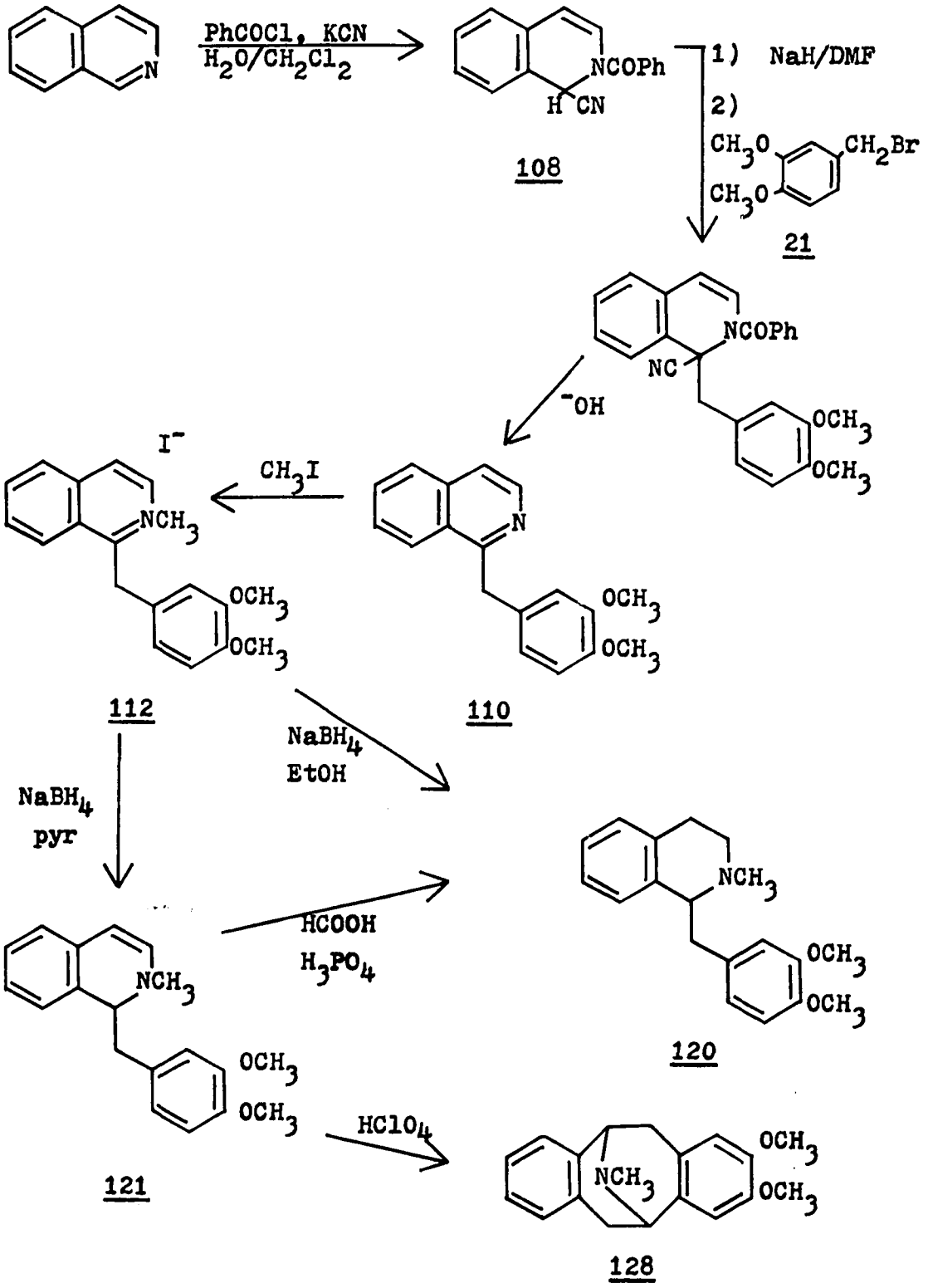
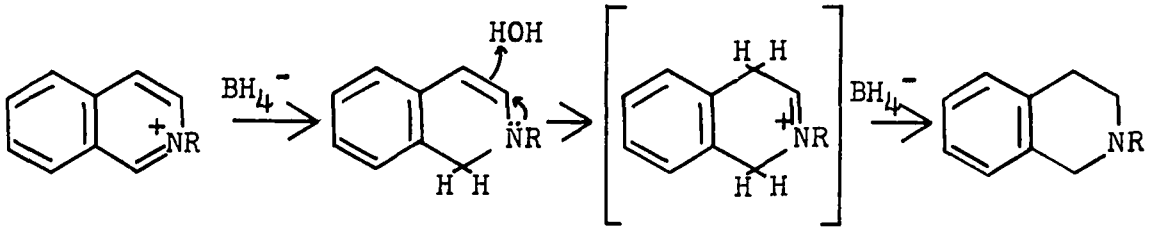


Figure 13. The Synthesis of Pavinane Alkaloids.



The third method that was considered was catalytic reduction of the isoquinolinium salts to the 1,2-dihydro compound. Grewe[54] found that reductions of isoquinolinium salts over Adams' catalyst in basic solution led to isolation of 1,2-dihydroisoquinolines rather than the fully reduced tetrahydroisoquinoline. When acid was added to the system, reduction proceeded to the tetrahydro stage. These results are also consistent with the mechanism of reduction proposed by Lyle and Anderson.[38]

The reduction of 112 with sodium borohydride in pyridine gave the 1,2-dihydro derivative, 121. Nmr spectroscopy confirmed the structure of this compound for there was an AB quartet centered at 6.58 ppm with a coupling constant of 7 Hz ($\Delta\nu_{AB}$ = 43.4 Hz) due to the resonance of the vinyl protons. In addition, the low field vinyl signal assigned to the proton in the 3-position showed meta coupling with the proton in the 1-position. The N-methyl signal appeared at 2.70 ppm and there was also a small signal at 2.46 ppm which indicated that a small amount of tetrahydro product was present. The nmr spectra of the 1,2-dihydroisoquinoline

derivatives were very similar to those published by Neumeyer[55] for 1,2-dihydroisoquinolines.

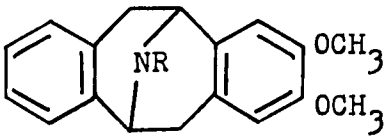
By using the classical synthetic approach of Battersby and Binks[24] of treating the 1,2-dihydroisoquinoline (121) with a mixture of formic acid and phosphoric acid, only the tetrahydro derivative, 120, was isolated. Products such as 120 resulting from disproportion have been isolated previously from the classical synthetic approach.[56] Treating 121 with a variety of proton sources, such as trichloroacetic acid, trifluoroacetic acid, p-toluenesulfonic acid, acid washed alumina or acid washed Dowex-50 ion exchange resin, yielded organic products which showed no signal in the nmr spectra assignable to an N-methyl group.

The disproportionation reaction of 1,2-dihydroisoquinolines leading to tetrahydroisoquinolines (120) has been shown to be a bimolecular process.[32] Recently, the rearrangement of 1-benzyl-1,2-dihydroisoquinolines to the 3-benzyl derivative has also been shown[33] to be bimolecular. The cyclization of 1-benzyl-1,2-dihydroisoquinoline to a pavine on the other hand must be unimolecular. This suggested that the desired cyclization could be favored over the other reactions by using a highly dilute reaction mixture. To test this hypothesis a dilute solution of 121 in chloroform was slowly added to a stirred mixture of chloroform and 70% aqueous perchloric acid. In this manner the 1-benzyl-1,2-dihydroisoquinoline, already in a dilute solution, would slowly diffuse through the chloroform layer and mix with the proton source at the interface of the aqueous and chloroform

layers. The molecule would undergo internal cyclization since there would be no other molecules in the vicinity with which it could react in a bimolecular process. After the addition was complete, stirring was continued for 72 hr. The layers were separated, and the aqueous layer was diluted to 1 l. with water. The perchlorate of 128 precipitated from solution and was collected by filtration. In this manner, a series of pavinane derivatives was synthesized (Table VII).

TABLE VII

Pavinane Derivatives



Compound	R	% Yield
128	CH_3	60
129	CH_2Ph	50
130	CH_2-4'-NO_2Ph	95
131	CH_2-2',6'-diClPh	58

When the two methoxyl groups were replaced with a methylenedioxy group, only highly colored materials were isolated from the reaction mixtures. This was not unexpected because of the knownlability of the methylenedioxy function under strongly acidic conditions.[57]

There have been several reports[28,32,58] that

1-benzyl-1,2-dihydroisoquinoline underwent rearrangement in preference to cyclization when treated with dilute acid. Shavel,[27] however, reports that with 1-skatyl-1,2-dihydroisoquinolines (151), cyclization occurs very readily while rearrangement could only be observed under special conditions of treatment with acid. 1-Skatylisoquinoline (149) was prepared from gramine and 1-cyano-2-benzoyl-1,2-hydroisoquinoline (108) and was subjected to Shavel's conditions for cyclization, 1N hydrochloric acid and methanol (Figure 14). In each attempt, the indole nucleus decomposed under the acidic conditions. When the high dilution technique described earlier was used with 1N hydrochloric acid and diethyl ether as solvents, a quantitative yield of 152 was realized.

Simultaneously, another approach to the 1,2-dihydroisoquinoline enamine system utilizing a 1-benzylisoquinolone (147) as precursor was attempted. One advantage of this system was that the resulting pavinane contained a secondary nitrogen. Various substituents could then be placed on the nitrogen in the last step. Figure 15 outlines this synthetic pathway.

2-Indanone (142) was prepared from technical grade indene by the procedure of Organic Syntheses.[59] Studies[60] on enamine reactions of 2-indanone indicated moderate yields of alkylation products had been obtained. Blomquist[60a] prepared 1-benzyl-1-indanone (145) in 20% yield from 142. Since 145 decomposed on distillation and was sensitive to air, a characteristic of 2-indanones, the oxime (146) was prepared directly from the crude reaction mixture of 145.

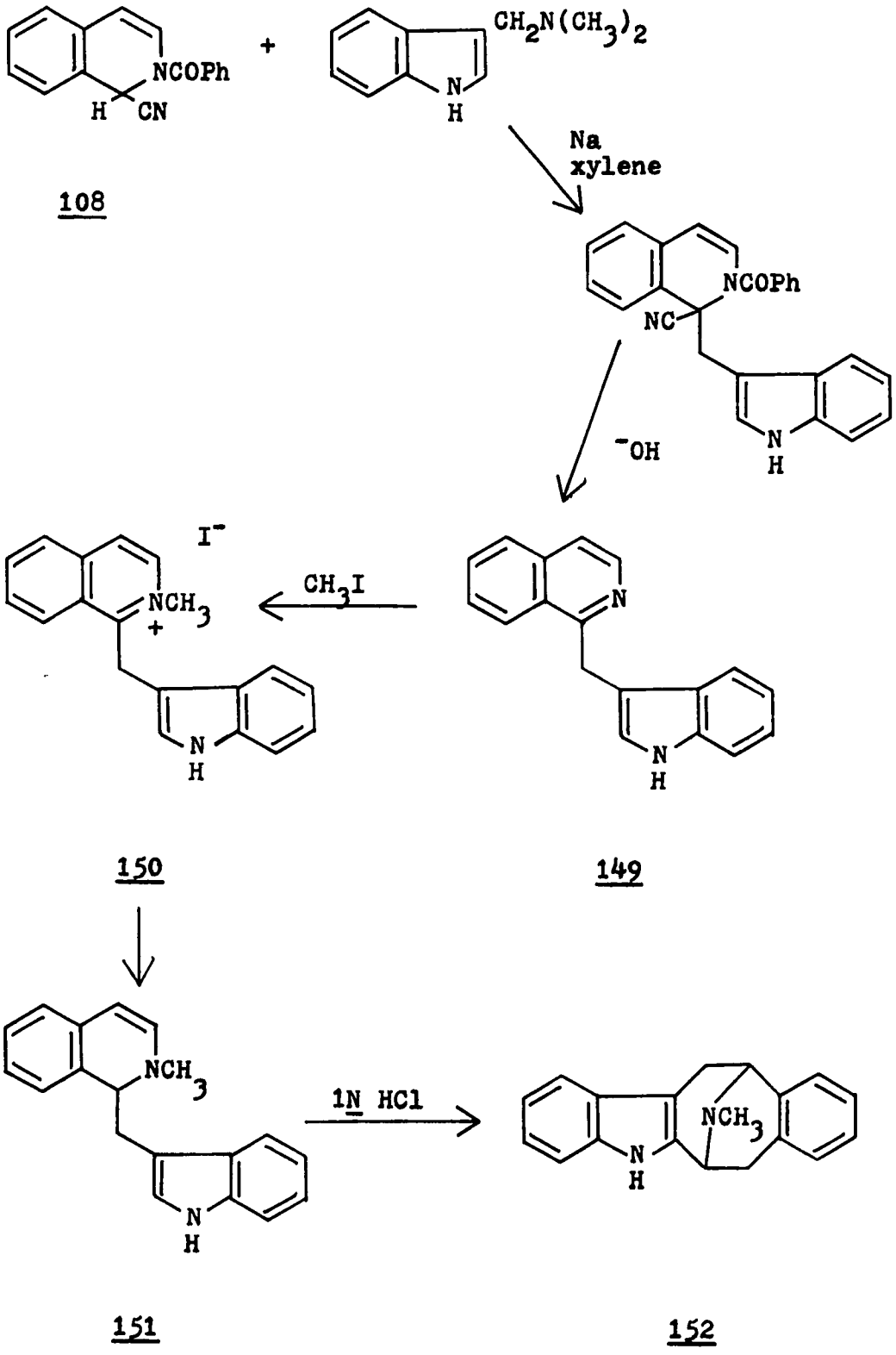


Figure 14. The Synthesis of an Indolopavinane Derivative.

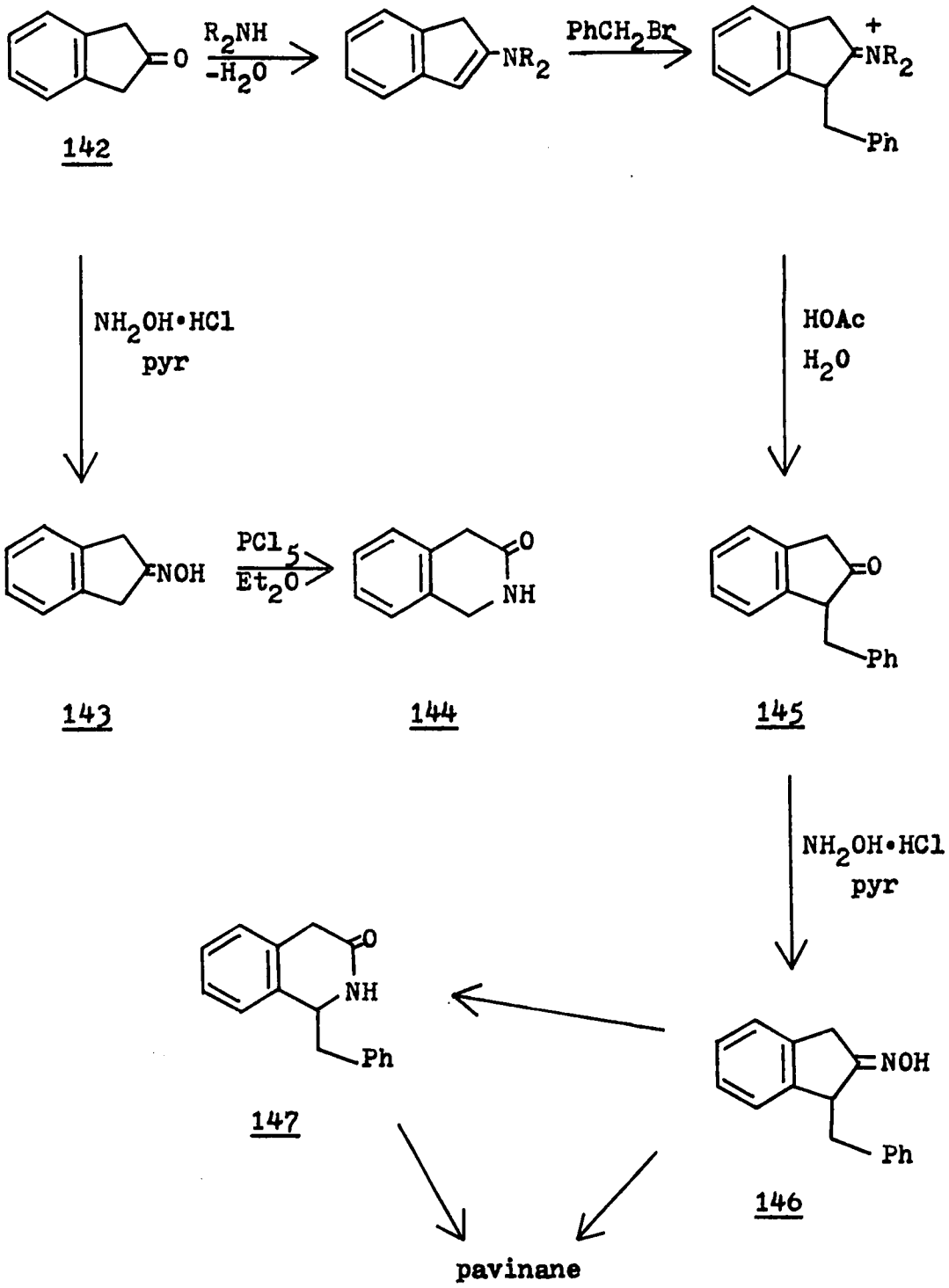


Figure 15. The Synthesis of 1,4-Dihydro-3-[2H]isoquinolone Derivatives.

As a model for the Beckmann rearrangement,[61] the oxime (143) of 2-indanone was prepared. When the Beckmann rearrangement was attempted in polyphosphoric acid (PPA), only tars were isolated. However, when phosphorous pentachloride in ether at room temperature was used, a 70% yield of 1,4-dihydro-3-[2H]isoquinolone (144) was realized. This reaction pathway provides a novel approach to the synthesis of 144.

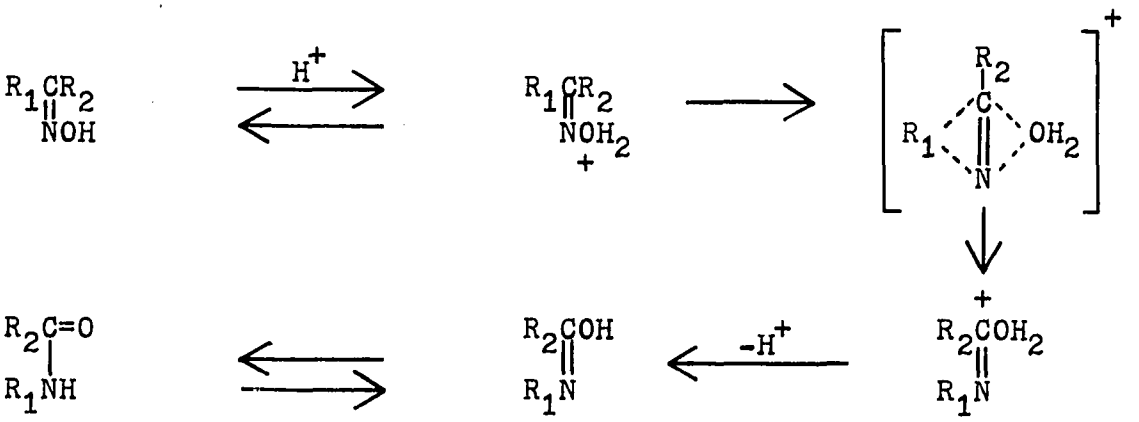
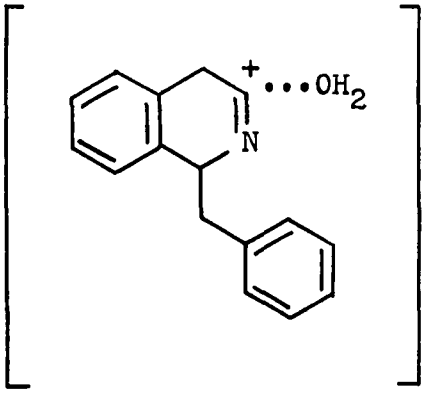


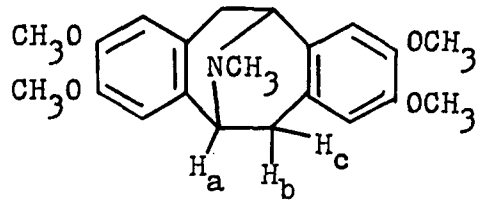
Figure 16. Mechanism for the Beckmann Rearrangement.



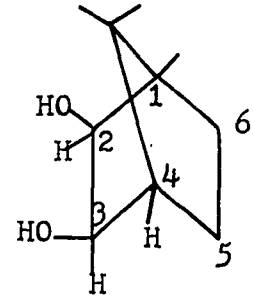
148

The mechanism of the Beckmann rearrangement (Figure 16) consists essentially of the formation of an electron-deficient nitrogen atom by the partial ionization of the oxygen-nitrogen bond of the oxime with a simultaneous intramolecular migration of the group anti to the departing hydroxyl group. In preparing 146, the most favored oxime isomer should have the hydroxyl group anti to the carbon bearing the benzyl substituent because of steric considerations. If the Beckmann rearrangement were performed on 146, one of the intermediates would have structure 148. It is conceivable that cyclization of the electron-rich, benzyl ring to the electron deficient carbon would take place to give a pavinane directly from the reaction mixture. Although this reaction sequence appeared to be a promising route to pavinane derivatives, work was stopped when the cyclization of 1-benzyl-1,2-dihydroisoquinolines was improved by the high dilution techniques.

The nmr spectra of pavinane derivatives having a C_2 axis exhibit striking symmetry[26,60,62] and are quite characteristic for this class of alkaloids. The nmr spectrum of argemonine (10a), for example, is in part an ABX system[63] in which proton H_a couples only with H_b and appears as a doublet centered at 4.08 δ (J_{ab} = 6 Hz). The signal for proton H_c is coupled only with proton H_b and appears as a doublet centered at 2.62 δ (J_{bc} = 17 Hz). The signal for proton H_b is split by H_a and H_c and is a pair of doublets centered at 3.53 and 3.42 δ. The signal for the aromatic protons give singlets at 3.92 and 3.84 δ. The N-methyl group is a singlet at 2.57 δ.

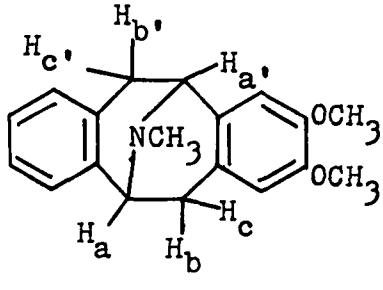


10a

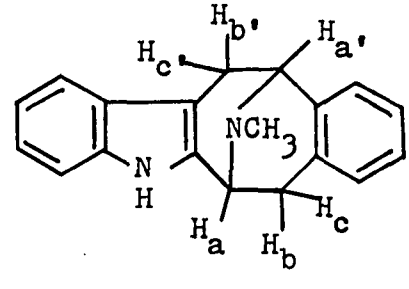


154

The lack of spin-spin splitting between H_a and H_c can be related to the phenomenon investigated by Anet[64] in the bicyclo[2.2.1]heptane system. Thus, 2-exo, 3-exo-camphane-2,3-diol (154) exhibits a coupling constant of zero ($J_{3,4} = 0$) between the bridgehead hydrogen and the adjacent proton, predicted by the Karplus equation[65] where the dihedral angle is 79°.



128



152

The pavinane derivatives prepared for this thesis were unsymmetrical (i.e. containing no C_2 axis[41]) analogs. For 128, the bridgehead hydrogens, H_a and $H_{a'}$, appear as two overlapping doublets ($J_{ab} = J_{a'b'} = 6$ Hz), centered at 4.13 and 4.07 δ respectively, H_c and $H_{c'}$, as two doublets ($J_{bc} = J_{b'c'} = 17$ Hz) centered at 2.58 and 2.70 δ respectively and H_b and $H_{b'}$, as two triplets between 3.69 and 3.32 δ. C_1-H and C_4-H appear as two singlets at 6.67 and 6.49 δ respectively and the N-methyl group is a singlet at 2.58 δ. Compounds 129, 130 and 131 all have benzyl substituents on nitrogen. The diastereotopic methylene hydrogens appear as an AB quartet ($J_{AB} = 6$ Hz, $\Delta\nu_{AB} = 9$ Hz). The coupling constants for the proton resonances of 152 are the same as for the unsymmetrical pavinanes; however, the chemical shifts of these signals are different. Table VIII lists the nmr data for the unsymmetrical pavinane derivatives prepared and these data agree favorably with published results.[27,31,66]

Studies of the uv spectra in methanol of pavinanes 128 through 131 and their proton salts indicated there were no intramolecular charge transfer interactions which could be observed. In the nmr spectra of the proton salts of 129 and 130 in d_6-acetone, the signals resulting from two isomers were present (Figure 17) in the aromatic region. Two distinct sets of equal intensity singlets were observable for the C_1-H and C_4-H. When compared with the spectrum of a commercial sample of DL-pavine hydrochloride (9) and with the spectrum of 128, one set of singlets was shifted downfield about 0.16 ppm. Compounds 128 and 131 showed only one set of

TABLE VIII

NMR Data for Pavinane Derivatives

Compound	H_a (J_{ab}=6Hz)	H_b	H_c (J_{bc}=17Hz)	NR	C_2-OCH_3	C_3-OCH_3	C_1-H	C_4-H
128	(d) 4.13* (d) 4.07	(t) 3.69 (t) 3.32	(d) 2.70 (d) 2.58	(s) 2.58	(s) 3.87	(s) 3.79	(s) 6.67	(s) 6.49
129	(d) 4.24 (d) 4.18	(m) 3.70-3.30	(d) 2.74 (d) 2.64	(q) 3.84 (J=6Hz)	(s) 3.82	(s) 3.76	(s) 6.62	(s) 6.50
130	(d) 4.18 (d) 4.08	(m) 3.68-3.28	(d) 2.76 (d) 2.72	(q) 3.95 (J=6Hz)	(s) 3.87	(s) 3.80	(s) 6.70	(s) 6.58
131	(d) 4.28 (d) 4.20	(m) 3.72-3.36	(d) 2.72 (d) 2.60	(q) 4.06 (J=6Hz, $\Delta\nu$=9Hz)	(s) 3.87	(s) 3.79	(s) 6.70	(s) 6.50
152	(d) 4.24 (d) 3.96	(m) 3.56-3.04	(d) 2.68	(s) 2.56		N-H 8.40		

* δ in ppm from TMS

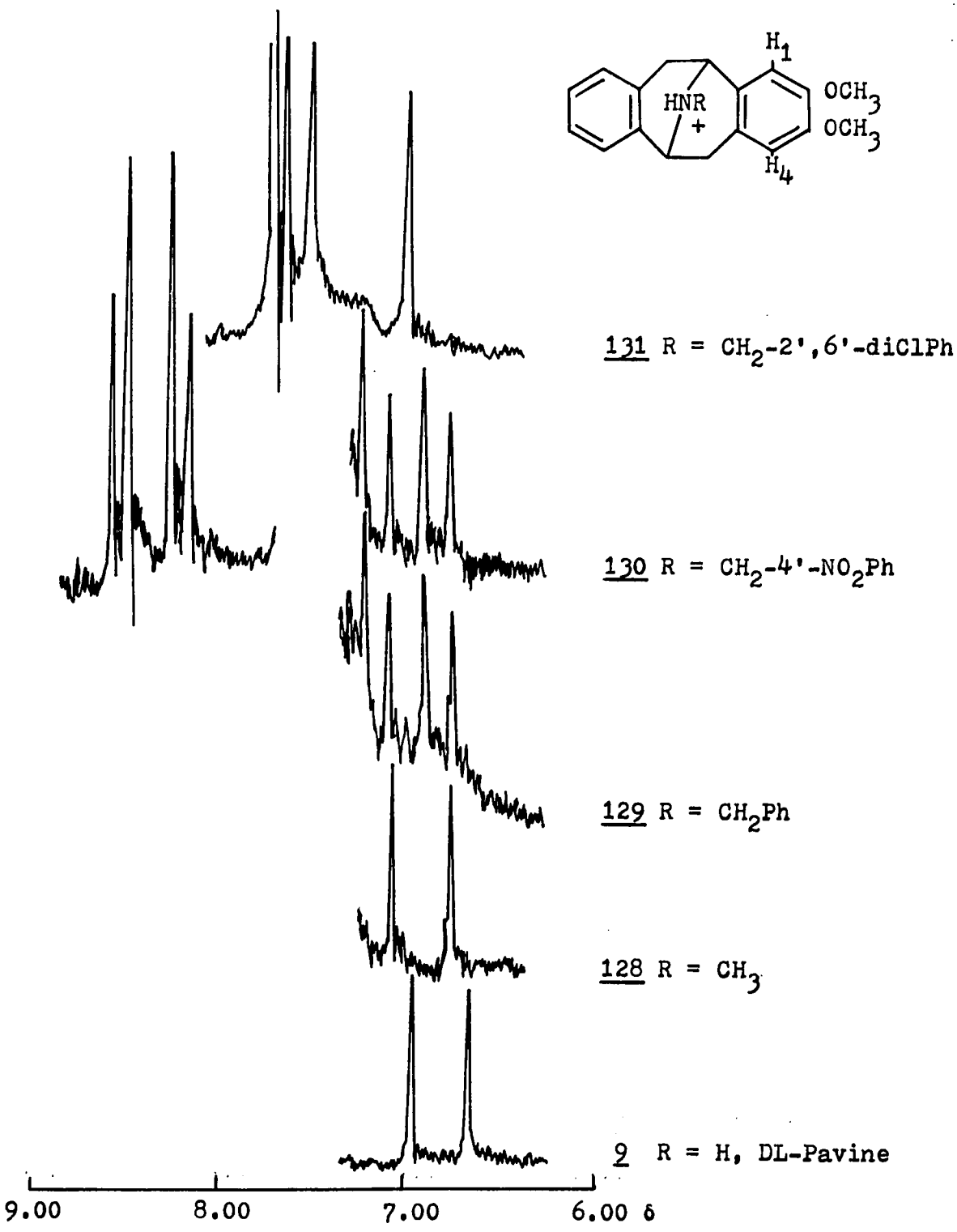
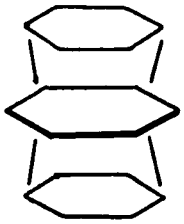


Figure 17. The NMR Spectra of Proton Salts of Pavinane Derivatives in d_6-Acetone.

singlets for C_1-H and C_4-H. For 131 one singlet was shifted downfield 0.16 ppm and the other singlet was shifted downfield 0.36 ppm when compared with 128.

House[67] has found for 1,8-diphenylnaphthalene (155) that a face-to-face interaction of the aromatic rings causes a shift in the aromatic signals of 0.5 ppm upfield. Studies[68] with paracyclophane (156) also gave evidence for the fact that protons which are located in the shielding cone of an aromatic ring are shifted upfield. The nmr data for the pavinanes indicate that the aromatic hydrogens at C_1 and C_4 lie in the deshielding cone[95] of the N-benzyl substituent.

Shielding Region



Deshielding Region

A Drieding model of 128 shows that the N-methyl group does not lie over an aromatic ring. Although two isomers are most likely formed when 128 is protonated, only one set of signals is observed. The N-benzyl group may or may not lie over an aromatic ring. When 129 or 130 are protonated, two isomers are observed due to the influence of the benzyl substituent on the chemical shifts of the ring hydrogen. This interaction, however, does not seem to result from a face-to-

face orientation of the aromatic rings.

The proton salt of 130 shows two sets of singlets for the C_1-H and C_4-H but only one set of signals (an AB quartet) for the p-nitrobenzyl aromatic ring. This observation is an indication that the unsubstituted aromatic ring and the dimethoxyl substituted aromatic ring of 130 are not sufficiently magnetically different to observably influence the p-nitrobenzyl aromatic system.

The fact that 131 shows only one set of singlets for the C_1-H and C_4-H and that these signals are shifted downfield indicates that one isomer was formed in large preference. That isomer would have the N-benzyl group located on the same side of the nitrogen atom as the dimethoxyl aromatic ring. Another explanation is that the signals for each isomer are accidently equivalent; however, this seems unlikely.

The uv data indicate that there are no observable intramolecular charge transfer interactions occurring in the pavinane series. The nmr and uv data together give good evidence that the conformation which has the benzyl substituent in a face-to-face orientation with the aromatic groups of the pavinane ring system is unfavored.

EXPERIMENTAL

General

Melting Points. Melting points were determined using a Thomas-Hoover apparatus and are uncorrected.

Infrared Absorption Spectra. The infrared spectra were determined using a Perkin-Elmer Model 137B Infracord spectrophotometer equipped with sodium chloride optics. The spectra of liquids were determined as films and the spectra of solids were run as potassium bromide pellets. The intensity of the bands are indicated by (s), strong; (b), broad; (m), medium; and (w), weak; and the location of each band is given in frequency units, cm^{-1}. Each spectrum was calibrated at 1601.4 cm^{-1} using a polystyrene film.

Nuclear Magnetic Resonance Spectra. The nuclear magnetic resonance spectra were determined using a Varian Model A-60 Spectrometer or a Jeol MH100 Spectrometer. The chemical shift data are reported as δ values in ppm from tetramethylsilane (TMS). When $DCCl_3$ was used as solvent, TMS was used as an internal standard; when d_6-DMSO, d_6-acetone or D_2O were used as solvents, TMS was used as an external standard. The integrations were determined by dividing the total integration by the theoretical number of protons and the number of protons responsible for each region of absorption was then determined using this calculated value for a proton.

Ultraviolet Absorption Spectra. The ultraviolet absorption spectra were determined using a Cary Model 15 recording spectrophotometer.

Elemental Analysis. Elemental analyses were determined by Linda Heavner, Gail Lambert or Dee Cardin using an F and M Model 180 carbon, hydrogen, and nitrogen analyzer.

Materials. A. Reagents: All chemicals were purchased from Aldrich Chemical Company and used without further purification except as noted. Methyl iodide and 30% aqueous methylamine were purchased from Fisher Chemical Company while phosphorus oxychloride was purchased from Allied Chemicals. Hydrogen bromide and hydrogen chloride (gases) were purchased from Baker Chemical Company, and N-bromosuccinimide was purchased from Eastman. Borane diethyletherate (1M in tetrahydrofuran), lithium aluminum hydride, sodium borohydride, and sodium hydride were purchased from Alfa Inorganics (Ventron). Lithium aluminum deuteride was purchased from Roth Laboratories (Germany), while platinum oxide was obtained from Engelhard Chemicals.

B. Solvents: The following solvents were used without additional purification: pentane, petroleum ether, hexane, cyclohexane, methanol, ethanol, isopropanol, carbon tetrachloride, chloroform, methylenechloride, benzene, toluene, xylene, ethylacetate, acetonitrile, drum ether and acetone. Dimethylformamide, glyme and tetrahydrofuran were distilled from calcium hydride and stored over 4A molecular sieves. Pyridine was distilled and stored over potassium

hydroxide pellets. Anhydrous ether was stored over sodium wire.

Preparation of Benzylcarbamate (157). Benzylcarbamate (157) was prepared from benzylchloroformate and concentrated ammonium hydroxide according to the Organic Syntheses procedure,[69] and 70% of 157 was obtained as white needles, mp 87-88° (benzene), lit.[69] mp 87°; ir (#13252, KBr) 3400 (m), 1700 (s), 1610 (m), 1460 (s), 1410 (b), 1360 (b), 1100 (m), 1080 (s), 920 (m), 740 (s).

Preparation of Methylenebisethylcarbamate (14). Compound 14 was prepared according to the procedure of Cava.[34] Ethylcarbamate (89 g, 1.0 mol) was dissolved in 500 ml of cold water, and 40.5 g (0.5 mol) of 37% aqueous formaldehyde and 1-2 ml of concentrated hydrochloric acid were added. The mixture was allowed to stand at ambient temperature for 3 days during which time 63.4 g (67%) of 14 was deposited as white needles, mp 130-132°, lit.[34] mp 127-130°; ir (#13430, KBr) 3400 (m), 1700 (s), 1510 (s), 1240 (b), 1110 (m), 1020 (s), 925 (m), 780 (m). This solid was used without further purification.

Preparation of Methylenebisbenzylcarbamate (158). Compound 158 was prepared from benzylcarbamate (157) according to the above procedure of Cava.[34] The biscarbamate (158) was obtained in 40% yield as a white solid, mp 149-158° (benzene), lit.[94] mp 149°; ir (#13431, KBr) 3400 (m), 1700 (s), 1510 (s), 1250 (m), 975 (m).

Preparation of 9,10-Dimethoxyanthracene (19). Compound 19 was prepared according to the procedure of Meek.[36] Anthraquinone (10.4 g, 0.5 mol) was ground with 5.0 g of zinc dust and placed in a reaction flask with 20 ml of ethanol. To this mixture was added 100 ml of 20% sodium hydroxide solution and the slurry was heated under reflux for 1 hr. Methyl p-toluenesulfonate was added slowly with stirring until the color of the solution changed from deep purple to orange. The resulting precipitate was collected by filtration and washed with alkaline sodium hydrosulfite. The solid was then dissolved in benzene and the solution was filtered and the filtrate concentrated to yield 9.6 g (81%) of 19 as yellow-green crystals, mp 196-200°, lit.[36] mp 198-199°; ir (#13165, KBr) 1610 (m), 1470 (s), 1300 (s), 1070 (b), 975 (s), 790 (s), 770 (s).

General Procedure for the Preparation of Substituted Benzyl Bromides. These compounds were prepared by the method of Baldwin.[70] A 300 ml three-necked flask fitted with a thermometer and gas inlet and outlet tubes was charged with 0.05 mol of the substituted benzyl alcohol in 100 ml of benzene. Hydrogen bromide gas was bubbled into the cooled solution. The reaction temperature rose from 4° to 11°. After 20 min, the temperature of the reaction mixture fell to 5° and the addition of hydrogen bromide was terminated. Anhydrous sodium sulfate was added, and the mixture was stirred for 4 hr. The reaction was filtered and the filtrate was evaporated to give the lachrymatory product as the residue.

The infrared spectrum showed an absence of OH stretching adsorption. The product was then used immediately without further purification except as noted.

4-Methoxybenzyl Bromide (20). The above procedure with p-methoxybenzyl alcohol gave 10.0 g (100%) of 20 as a pink oil,[70] ir (#11526, film) 1620 (s), 1590 (m), 1515 (s), 1475 (m), 1440 (m), 1310 (s), 1260 (b), 1240 (m), 1210 (m), 1190 (s), 1045 (b), 840 (b).

3,4-Dimethoxybenzyl Bromide (21). The above procedure with 3,4-dimethoxybenzyl alcohol gave 11.5 g (100%) of 21 as a pink oil which solidified on cooling. The solid was recrystallized from low boiling petroleum ether to give 8.0 g (70%) of 21 as a white solid, mp 56-58°. The literature[71a] reports using this compound as an oil without further purification; ir (#12196, KBr) 2950 (w), 1660 (m), 1500 (s), 1460 (s), 1340 (s), 1260 (b), 1210 (m), 1150 (b), 1025 (b), 850 (s), 820 (b), 760 (s); nmr (#10303, $DCCl_3$) δ 6.80 (m, 3H), 4.40 (s, 2H), 3.76 (s, 6H).

3,4-Methylenedioxybenzyl Bromide (22). The above procedure with 3,4-methylenedioxybenzyl alcohol gave 10.8 g (100%) of 22 as a clear oil which solidified on cooling. The solid was recrystallized from low boiling petroleum ether to give 9.0 g (86%) of 22 as a white solid, mp 43.5-45.5°, lit.[71b] mp 48°; ir (#12215, KBr) 1600 (w), 1500 (s), 1460 (s), 1380 (m), 1260 (s), 1110 (m), 1050 (s), 940 (s), 870 (m), 820 (b), 770 (m), 730 (w); nmr (#10373, $DCCl_3$) δ 6.79 (m, 3H),

5.87 (s, 2H), 4.43 (s, 2H).

Preparation of 2,4-Dinitrobenzyl Bromide (23). Preparation of 23 was carried out by the method of Bauer.[72] In a 500 ml round-bottomed flask equipped with a reflux condenser and magnetic stirrer was placed 18.2 g (0.1 mol) of 2,4-dinitrotoluene, 17.8 g (0.1 mol) of N-bromosuccinimide, 0.1 g of dibenzoylperoxide and 175 ml of carbon tetrachloride. The mixture was heated under reflux with stirring under a 100 watt incandescent light overnight. The mixture was cooled and the succinimide was removed by filtration. The brown carbon tetrachloride filtrate was washed with 50 ml of 5% sodium hydroxide and 50 ml of water, and was dried over anhydrous magnesium sulfate. After filtration and evaporation of the filtrate, a light yellow oil remained. An analysis of the nmr spectrum showed that the oil was a mixture of 70 mol % of 23 and 30 mol % of starting material; nmr (#12083, $DCCl_3$) δ 7.82-6.68 (m), 4.07 (s), 1.97 (s). This mixture was used without any further purification.

Preparation of 6,7-Dimethoxy-3,4-dihydroisoquinoline (24). Compound 24 was prepared in 94% yield from β-(3,4-dimethoxyphenyl)ethylamine by the method of Popp and McEwen.[73] The amine (10 g, 0.06 mol) and 7 g (0.15 mol) of 97% formic acid were heated at 170-180° for 3.5 hr. The resulting N-formyl derivative was dissolved in 50 ml of dry toluene, 30 ml (50 g, 0.33 mol) of phosphorous oxychloride was added, and the mixture was heated under reflux for 1 hr. The reaction was then diluted with 150 ml of petroleum ether (bp 40-60°C), the

solvent was decanted from the brown gum, 100 ml of 10% hydrochloric acid was cautiously added, and the non-basic impurities were extracted twice with 30 ml of benzene. The acidic layer was made basic with sodium hydroxide and was extracted four times with 50 ml of benzene. The combined benzene extracts were dried over anhydrous potassium carbonate and filtered and the filtrate was evaporated to yield 9.9 g (94%) of 24 as a brown oil. The picrate, mp 207-209°d (ethanol), lit.[73] mp 207-208°, was prepared; ir (#11342, film) 2950 (m), 1630 (s), 1600 (s), 1585 (s), 1470 (s), 1360 (s), 1330 (s), 1290 (s), 1285 (m), 1250 (s), 1225 (m), 1200 (m), 1120 (s), 1030 (m), 1000 (m), 950 (w), 890 (m), 825 (m), 785 (m); nmr (#12057, $DCCl_3$) δ 7.89 (t, J = 1.8 Hz, 1H), 6.54 (s, 1H), 6.41 (s, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.70-3.40 (m, 1H), 2.90-2.36 (m, 2H). This brown oil was used without further purification.

General Procedure for the Preparation of Isoquinolinium Salts. In a 100 ml round-bottomed flask equipped with a reflux condenser and a calcium chloride drying tube was placed 0.02 mol of the appropriately substituted isoquinoline and 0.02 mol of methyl iodide or the benzyl halide dissolved in 35 ml of dry tetrahydrofuran. The solution was heated under reflux with stirring overnight. The solid which precipitated was removed by filtration, washed with ether and dried. The product was recrystallized and spectral and analytical data were obtained on the recrystallized solid.

2-Methylisoquinolinium Iodide (25). The above procedure with isoquinoline and methyl iodide gave 4.2 g (78%) of

25 as a pale yellow solid, mp 161-162° (isopropanol), lit.[74] mp 158-161°; ir (#11570, KBr) 2950 (w), 1650 (w), 1350 (w), 1280 (m), 820 (s), 760 (b).

2-Benzylisoquinolinium Bromide (26). The above procedure with isoquinoline and benzyl bromide gave 5.6 g (91%) of 26 as a white solid, mp 112-113° (isopropanol), lit.[75] mp 110-111.5°; ir (#11571, KBr) 3400 (m), 2950 (w), 1640 (s), 1460 (m), 1385 (b), 1170 (m), 1110 (m), 980 (m), 885 (m), 820 (s), 785 (m), 770 (s), 725 (b).

2-(2',6'-Dichlorobenzyl)isoquinolinium Chloride (27). The above procedure with isoquinoline and 2,6-dichlorobenzyl chloride gave 4.3 g (66%) of 27 as a white solid, mp 227-230°d (ethanol-ether); ir (#11484, KBr) Appendix, A-1.

Anal. Calcd for $C_{16}H_{12}NCl_3$: C, 59.19; H, 3.72; N, 4.31. Found: C, 59.11; H, 3.88; N, 4.37.

2-(2',4'-Dinitrobenzyl)isoquinolinium Bromide (28). The above procedure with isoquinoline and 23 gave 5.8 g (75%) of 28 as a pale yellow solid, mp 183-184° (ethanol), lit.[76] mp 151.5°; ir (#11480, KBr) 3400 (s), 3000 (b), 1640 (s), 1600 (s), 1570 (b), 1400 (s), 1350 (b), 1200 (w), 1170 (m), 1130 (w), 1070 (w), 1050 (w), 1000 (w), 930 (m), 900 (m), 845 (b), 805 (s), 770 (b), 740 (s), 715 (w).

Anal. Calcd for $C_{16}H_{12}BrN_3O_4$: C, 49.24; H, 3.10; N, 10.76. Found: C, 49.34; H, 3.18; N, 10.58.

2-(4'-Methoxybenzyl)isoquinolinium Bromide (29). The

above procedure with isoquinoline and 20 gave 6.4 g (97%) of 29 as a white solid, mp 239-241°, lit.[70] mp 235-236°; ir (#11547, KBr) 1950 (m), 1640 (w), 1600 (m), 1500 (m), 1440 (m), 1400 (m), 1305 (w), 1290 (m), 1270 (s), 1195 (s), 1015 (s), 950 (w), 890 (w), 865 (m), 845 (b), 785 (m), 760 (b).

2-(3',4'-Dimethoxybenzyl)isoquinolinium Bromide (30). The above procedure with isoquinoline and 21 gave 6.4 g (89%) of 30 as a yellow-green solid, mp 213-216° (ethanol); ir (#11563, KBr) Appendix, A-2.

Anal. Calcd for $C_{18}H_{18}BrNO_2$: C, 60.00; H, 5.03; N, 3.88. Found: C, 60.35; H, 4.99; N, 3.89.

2-Benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Bromide (31). The above procedure with 24 and benzyl bromide gave 5.2 g (72%) of 31 as a yellow solid, mp 192-196°d (ethanol-ether), lit.[77] mp 192-195°d; ir (#11469, KBr) 2950 (s), 1650 (s), 1600 (s), 1550 (s), 1500 (s), 1450 (s), 1400 (w), 1350 (s), 1300 (s), 1260 (s), 1240 (m), 1200 (w), 1130 (s), 1090 (m), 1000 (s), 990 (m), 945 (w), 920 (w), 870 (m), 845 (m), 790 (m), 745 (m), 710 (b).

2-(2',6'-Dichlorobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium Chloride (32). The above procedure with 24 and 2,6-dichlorobenzyl chloride gave 5.2 g (67%) of 32 as a yellow solid, mp 180-182°d (ethanol-ether); ir (#11470, KBr) Appendix, A-3.

Anal. Calcd for $C_{18}H_{18}Cl_3NO_2$: C, 55.90; H, 4.69; N, 3.62. Found: C, 55.90; H, 4.84; N, 3.47.

2-Methyl-5-nitroisoquinolinium Iodide (33). The above procedure with 5-nitroisoquinoline and methyl iodide gave 5.2 g (83%) of 33 as orange needles, mp 196-198°d (ethanol-isopropanol), lit.[78] mp 188-190°d; ir (#11495, KBr) 2950 (m), 1630 (m), 1530 (s), 1350 (s), 1285 (m), 1175 (m), 1015 (w), 925 (w), 855 (w), 840 (w), 820 (m), 800 (w), 750 (m).

2-Benzyl-5-nitroisoquinolinium Bromide (34). The above procedure with 5-nitroisoquinoline and benzyl bromide gave 5.1 g (74%) of 34 as a yellow-green solid, mp 214-219°d (acetonitrile); ir (#11465, KBr) Appendix, A-4.

Anal. Calcd for $C_{16}H_{13}BrN_2O_2$: C, 55.66; H, 3.79; N, 8.11. Found: C, 55.55; H, 3.84; N, 8.19.

2-(4'-Methoxybenzyl)-5-nitroisoquinolinium Bromide (35). The above procedure with 5-nitroisoquinoline and 20 gave 5.6 g (75%) of 35 as deep gold needles, mp 197-199°d, after recrystallization from acetonitrile-ethyl acetate; ir (#11548, KBr) Appendix, A-5.

Anal. Calcd for $C_{17}H_{15}BrN_2O_3$: C, 54.41; H, 4.02; N, 7.46. Found: C, 54.16; H, 3.87; N, 7.65.

2-(3',4'-Dimethoxybenzyl)-5-nitroisoquinolinium Bromide (36). The above procedure with 5-nitroisoquinoline and 21 gave 7.1 g (88%) of 36 as an orange solid, mp 217-218°d (ethanol-water); ir (#11564, KBr) Appendix, A-6.

Anal. Calcd for $C_{18}H_{17}BrN_2O_4$: C, 53.34; H, 4.22; N, 6.91. Found: C, 53.22; H, 4.13; N, 6.70.

General Procedure for the Preparation of 1,2,3,4-Tetrahydroisoquinolines. In a 125 ml Erlenmeyer flask was placed 0.01 mol of the appropriately substituted isoquinolinium salt dissolved in 75 ml of ethanol. Sodium borohydride (1.8 g, 0.05 mol) was slowly added, and the reaction mixture was stirred at room temperature overnight. The excess sodium borohydride was decomposed with 10% hydrochloric acid, and the solution was concentrated. The residue was dissolved in 200 ml of water. The solution was filtered, and the filtrate was made basic with sodium bicarbonate. The aqueous solution was extracted three times with 50 ml of ether, and the combined ether extracts were dried over anhydrous potassium carbonate. After filtration and evaporation of the ether solution, spectral and analytical data were obtained on the resulting base. If the product was an oil, the hydrochloride was prepared by bubbling hydrogen chloride gas through an etheral solution of the base, and an analytical sample was prepared from the resulting solid.

2-Methyl-1,2,3,4-tetrahydroisoquinoline (38). The above procedure with 25 gave 0.8 g (54%) of 38 as a yellow oil, the hydrochloride of which melted at 225-227°(isopropanol-ether), lit.[79] mp 228°; uv max (#847, CH_3OH) hydrochloride 270 nm (ϵ240), 263 nm (ϵ250); ir (#11581, film) 2950 (m), 2800 (s), 1495 (w), 1450 (m), 1390 (s), 1295 (m), 1260 (w), 1250 (w), 1140 (m), 1100 (s), 1040 (m), 990 (w), 945 (s), 850 (w), 745 (b); nmr (#14760, $DCCl_3$) δ 7.05 (m, 4H); 3.51 (s, 2H), 3.04-2.46 (m, 4H), 2.37 (s, 3H).

2-Methyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (53). The above procedure with 33 gave 1.2 g (65%) of 53 as a yellow oil, the hydrochloride of which melted at 274° (ethanol-water), lit.[78] mp 260°; uv max (#854, CH_3OH) hydrochloride 255 nm (ε5000); ir (#11540, film) 2950 (m), 2800 (m), 1650 (w), 1530 (s), 1460 (s), 1350 (s), 1290 (m), 1240 (w), 1195 (w), 1130 (s), 1050 (m), 1000 (m), 970 (m), 915 (m), 845 (s), 815 (b), 780 (w), 740 (b); nmr (#14609, $DCCl_3$) δ 7.43 (m, 1H), 7.00 (s, 1H), 6.93 (s, 1H), 3.44 (s, 2H), 3.15-2.35 (m, 4H), 2.30 (s, 3H).

2-Benzyl-1,2,3,4-tetrahydroisoquinoline (39). The above procedure with 26 gave 1.8 g (80%) of 39 as a light yellow oil, the hydrochloride of which melted at 208-209° (ethanol-ether), lit.[80] mp 199-202°; uv max (#846, CH_3OH) hydrochloride 270 nm (ε310), 267 nm (ε400), 261 nm (ε550) 256 nm (ε480); ir (#11344, film) 2950 (m), 2800 (m), 2700 (m), 1500 (s), 1460 (s), 1360 (m), 1340 (m), 1305 (w), 1275 (w), 1240 (w), 1195 (w), 1140 (m), 1095 (m), 1060 (w), 1055 (m), 980 (w), 935 (s), 860 (w), 820 (w), 745 (b), 700 (b); nmr (#12058, $DCCl_3$) δ 7.02 (m, 5HO, 6.75 (m, 4H), 3.47 (s, 2H), 3.44 (s, 2H), 2.92-2.35 (m, 4H).

2-(2',6'-Dichlorobenzyl)-1,2,3,4-tetrahydroisoquinoline (40). The above procedure with 27 gave 1.4 g (48%) of 40 as a white solid, mp 87-88° (ethanol); uv max (#1026, CH_3OH) 271 nm (ε700), 263 nm (ε750); ir (#11485, KBr) Appendix, A-7; nmr (#12170, $DCCl_3$) Appendix, B-1.

Anal. Calcd for $C_{16}H_{15}Cl_2N$: C, 65.76; H, 5.17; N, 4.79. Found: C, 65.84; H, 5.16; N, 4.82.

2-(4'-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (43). The above procedure with 29 gave 1.1 g (45%) of 43 as a clear oil, the hydrochloride of which melted at 208-210° (isopropanol); uv max (#1024, CH_3OH) 270 nm (ϵ1500); ir (#11530, film) Appendix, A-8; nmr (#14594, $DCCl_3$) Appendix B-2.

Anal. Calcd for $C_{17}H_{20}ClNO$: C, 70.45; H, 6.95; N, 4.83. Found: C, 70.43; H, 7.02; N, 4.93.

2-(3',4'-Dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (44). The above procedure with 30 gave 2.0 g (71%) of 44 as a clear oil, the hydrochloride of which melted at 219-221° (isopropanol-ether); uv max (#1025, CH_3OH) hydrochloride 276 nm (ϵ3200); ir (#11567, film) Appendix, A-9; nmr (#14704, $DCCl_3$) Appendix, B-3.

Anal. Calcd for $C_{18}H_{22}ClNO_2 \cdot 0.25\ H_2O$: C, 66.65; H, 6.99; N, 4.32. Found: C, 66.96; H, 7.00; N, 4.28.

2-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (48). The above procedure with 31 gave 2.8 g (100%) of 48 as a white solid, mp 87-89° (hexane-benzene), lit.[77] mp 88-90°; uv max (#842, CH_3OH) 284 nm (ϵ3800); ir (#11482, KBr) 2800 (m), 1600 (m), 1520 (s), 1470 (s), 1390 (w), 1375 (m), 1350 (m), 1320 (w), 1295 (m), 1260 (s), 1240 (s), 1145 (s), 1105 (m), 1030 (m), 995 (w), 975 (w), 865 (m), 800 (m), 760 (m), 745 (m), 700 (w); nmr (#12184, $DCCl_3$) δ 7.32 (s, 5H), 6.58 (s, 1H), 3.80 (s, 3H, 3.77 (s, 3H), 3.66 (s, 2H), 3.53 (s, 2H), 2.76 (s, 4H).

2-(2',6'-Dichlorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (49). The above procedure with 32 gave 2.5 g (70%) of 49 as a white solid, mp 138-140°(ethanol); uv max (#1027, CH_3OH) 370 nm (ϵ100), 280 nm (ϵ3900); ir (#11481, KBr) Appendix, A-10; nmr (#12185, $DCCl_3$) Appendix, B-4.

Anal. Calcd for $C_{18}H_{19}Cl_2NO_2$: C, 61.37; H, 5.43; N, 3.97. Found: C, 61.57; H, 5.28; N, 3.97.

2-Benzyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (54). The above procedure with 34 gave 1.3 g (50%) of 54 as a yellow oil, the hydrochloride of which melted at 232-236°d (acetonitrile); uv max (#853, CH_3OH) hydrochloride 256 nm (ϵ5500); ir (#11462, film) Appendix, A-11; nmr (#12830, $DCCl_3$) Appendix, B-5.

Anal. Calcd for $C_{16}H_{17}ClN_2O_2 \cdot 0.25\ H_2O$: C, 62.13; H, 5.70; N, 9.05. Found: C, 61.91; H, 5.56; N, 9.07.

2-(4'-Methoxybenzyl)-5-nitro-1,2,3,4-tetrahydroisoquinoline (55). The above procedure with 35 gave 2.3 g (76%) of 55 as a light brown oil, the hydrochloride of which melted at 223-225°d (acetonitrile); uv max (#852, CH_3OH) hydrochloride 257 nm (ϵ5700); ir (#11539, film) Appendix, A-12; nmr (#14608, $DCCl_3$) Appendix, B-6.

Anal. Calcd for $C_{17}H_{19}ClN_2O_3 \cdot 0.25\ H_2O$: C, 60.17; H, 5.79; N, 8.26. Found: C, 60.50; H, 5.70; N, 8.26.

2-(3',4'-Dimethoxybenzyl)-5-nitro-1,2,3,4-tetrahydroisoquinoline (56). The above procedure with 36 gave 0.6 g

(25%) of 56 as a red oil, the hydrochloride of which melted at 268°d; uv max (#855, CH_3OH) hydrochloride 235 nm (ε11,500); ir (#11566, film) Appendix, A-13; nmr (#14705, $DCCl_3$) Appendix, B-7.

Anal. Calcd for $C_{18}H_{21}ClN_2O_4$: C, 59.25; H, 5.80; N, 7.68. Found: C, 59.48; H, 5.74; N, 7.58.

Preparation of 1,2,3,4-Tetrahydroisoquinoline (37). Concentrated hydrochloric acid was added to a solution of 10 g (0.08 mol) of isoquinoline in 100 ml of ethanol until the solution was acidic to pH paper. Platinum oxide (0.2 g) was added and the mixture was hydrogenated in a low pressure Parr hydrogenation apparatus. After 10 hr there was an uptake of 13 psi of hydrogen (theoretical = 14 psi) and the reaction was stopped. The catalyst was removed by filtration and the filtrate was evaporated to yield a gray solid. One recrystallization of the solid from isopropanol gave 9.2 g (70%) of 37·HCl as a white solid, mp 197-200°, lit.[79] mp 195-197°. The hydrochloride of 37 was dissolved in water and the solution was made basic with sodium hydroxide. The base was extracted into three 25 ml portions of ether and the combined ether extracts were dried over anhydrous barium oxide. After filtration and evaporation of the filtrate, 6.4 g (62%) of 37 as a clear oil remained; ir (#11387, film) 3300 (m), 3000 (m), 2900 (s), 1495 (s), 1450 (s), 1305 (m), 1260 (w), 1230 (w), 1190 (w), 1150 (s), 1040 (m), 965 (m), 950 (m), 750 (b); nmr (#12242, $DCCl_3$) δ 7.22-6.72 (m, 4H), 3.84 (s, 2H), 3.11-2.46 (m, 4H), 1.82 (s, 1H). This oil was used without further purification.

Preparation of 6,7-Dimethoxy-1,2,3,4-Tetrahydroisoquinoline (46). To 19.2 g (0.1 mol) of 6,7-dimethoxy-3,4-dihydroisoquinoline dissolved in 200 ml of ethanol was added concentrated hydrochloric acid until the solution was acidic to pH paper. Platinum oxide (0.3 g) was added and the mixture was hydrogenated in a low pressure Parr hydrogenation apparatus. After 1 hr there was an uptake of 17 psi of hydrogen (theoretical = 18 psi) and the reaction was stopped. To dissolve the hydrochloride of 46 that had precipitated during the reaction, 200 ml of ethanol was added, the solution was heated, and the catalyst was removed by filtration. On cooling the filtrate, 19.1 g (83%) of 46·HCl as a white solid, mp 254-256°d (ethanol), lit.[82] mp 251-252°, crystallized. The hydrochloride of 46 was dissolved in water and the solution was made basic with sodium hydroxide. The base was extracted into three 25 ml portions of benzene and the combined benzene extracts were dried over anhydrous barium oxide. After filtration and evaporation of the filtrate, 46 remained as a white solid, mp 84-87° (ethanol-petroleum ether), lit.[82] mp 84-85°; ir (#11483, KBr) 3300 (m), 2950 (m), 2800 (m), 1600 (m), 1510 (s), 1480 (b), 1370 (m), 1300 (w), 1265 (s), 1240 (s), 1100 (s), 1015 (m), 950 (w), 910 (w), 860 (s), 815 (s); nmr (#12327, $DCCl_3$) δ 6.34 (s, 1H), 6.26 (s, 1H), 3.75 (s, 2H), 3.67 (s, 6H), 3.15-2.40 (m, 4H), 1.86 (s, 1H).

General Procedure for the Preparation of 2-(Nitrobenzyl)-1,2,3,4-tetrahydroisoquinolines. Sodium hydride

(1.3 g, 0.03 mol) of 56% in oil was washed with two portions of pentane and the pentane was discarded. The appropriately substituted 1,2,3,4-tetrahydroisoquinoline (0.02 mol) dissolved in 50 ml of dry glyme was added dropwise to the stirred slurry of sodium hydride in 25 ml of glyme. After stirring at room temperature for 1 hr, 0.02 mol of methyl iodide or the appropriately substituted nitrobenzyl bromide dissolved in 25 ml of glyme was added dropwise over a 0.5 hr period. After stirring the slurry at room temperature for an additional 2 hr, the excess sodium hydride was decomposed with acetic acid. The mixture was concentrated, water was added, the acidic solution was made basic with sodium bicarbonate, and the aqueous solution was extracted three times with 25 ml of ether. The combined ether extracts were dried over anhydrous sodium sulfate and filtered, and the filtrate was evaporated to yield the base.

2-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (47). The above procedure with 46 and methyl iodide gave 2.5 g (61%) of 47 as a white solid, mp 72-75° (hexane), lit.[79] mp 75-77°, the hydrochloride of which melted at 204-208° (isopropanol), lit.[79] mp 215°; uv max (#832, 1023, CH_3OH) base 282 nm (ϵ4000), (#831, 865, CH_3OH) hydrochloride 283 nm (ϵ3400); ir (#11500, KBr) 3400(m), 2950 (m), 2800 (m), 1600 (m), 1515 (s), 1480 (s), 1380 (m), 1360 (m), 1340 (w), 1270 (s), 1230 (s), 1200 (w), 1150 (s), 1115 (s), 1070 (w), 1025 (s), 945 (w), 910 (b), 845 (b), 800 (m), 755 (m); nmr (#11452, $DCCl_3$) δ 6.39 (s, 1H), 6.31 (s, 1H), 3.72 (s, 6H),

3.38 (s, 2H), 2.80-2.46 (m, 4H), 2.35 (s, 3H).

2-(4'-Nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (41). The above procedure with 37 and p-nitrobenzyl bromide gave 4.0 g (75%) of 41 as a white solid, mp 59-61° (petroleum ether), the hydrochloride of which melted at 245-248°d (ethanol); uv max (#1035, CH_3OH) base 265 nm (ϵ11,100), (#860, CH_3OH) hydrochloride 256 nm (ϵ11,100); ir (#11488, KBr) Appendix, A-14; nmr (#12279, $DCCl_3$) Appendix, B-8.

Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.61; H, 6.01; N, 10.44. Found: C, 71.70; H, 6.06; N, 10.34.

2-(2',4'-Dinitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (42). The above procedure with 37 and 23 gave 1.8 g (27%) of 42 as orange needles, mp 112-113° (ethanol); ir (#11489, KBr) Appendix, A-15; nmr (#12308, $DCCl_3$) Appendix, B-9.

Anal. Calcd for $C_{16}H_{15}N_3O_4$: C, 61.33; H, 4.82; N, 13.41. Found: C, 61.62; H, 5.00; N, 13.33.
The hydrochloride was isolated as a white solid, mp 181-191° (isopropanol); uv max (#859, CH_3OH) hydrochloride 235 nm (ϵ17,800).

2-(4'-Nitrobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (50). The above procedure with 46 and p-nitrobenzyl bromide gave 2.3 g (35%) of 50 as a pale yellow solid, mp 119-121° (ethanol), the hydrochloride of which melted at 231-233°d (ethanol); uv max (#833, CH_3OH) base 276 nm (ϵ12,000), (#829, 861, CH_3OH) hydrochloride 260 nm

(ε11,300), 235 nm (ε11,000); ir (#11498, KBr) Appendix, A-16; nmr (#12333, $DCCl_3$) Appendix, B-10.

Anal. Calcd for $C_{18}H_{20}N_2O_4$: C, 65.85; H, 6.14; N, 8.53. Found: C, 65.74; H, 6.11; N, 8.48.

2-(2',4'-Dinitrobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (51). The above procedure with 46 and 23 gave 3.5 g (45%) of 51 as a yellow solid, mp 55-79° (ethanol), which slowly decomposed on standing. The hydrobromide melted at 208-212°d (ethanol); uv max (#838, 862, CH_3OH) hydrobromide 232 nm (ε24,800); ir (#11499, KBr) hydrobromide Appendix, A-17; nmr (#12614, $DCCl_3$) Appendix, B-11.

Anal. Calcd for $C_{18}H_{20}BrN_3O_6$: C, 47.58; H, 4.43; N, 9.24. Found: C, 47.49; H, 4.35; N, 9.59.

Preparation of 2,2-Dimethyl-1,2,3,4-tetrahydroisoquinolinium Iodide (57). A solution of 0.49 g (3.3 mmol) of 2-methyl-1,2,3,4-tetrahydroisoquinoline and 2.9 g (10 mmol) of methyl iodide in 5 ml of diethylether was let stand overnight at ambient temperature. The resulting white solid was collected by filtration and recrystallized from isopropanol to give a quantitative yield of 57, mp 191-193°, lit.[83] mp 191°; ir (#12755, KBr) 3000(w), 1460 (b), 1020 (w), 980 (w), 920 (s), 770 (s), 750 (m); nmr (#15312, D_2O) δ 7.30 (m, 4H), 4.51 (s, 2H), 3.65 (m, 2H), 3.16 (s, 8H).

General Procedure for the Preparation of Amides of 1,2,3,4-Tetrahydroisoquinolines. A mixture of 0.15 mol of the 1,2,3,4-tetrahydroisoquinoline and 0.17 mol of an acid

chloride was vigorously stirred in 25 ml of aqueous sodium hydroxide for 1 hr. The mixture was then extracted three times with 25 ml of methylene chloride and the combined extracts were washed twice with 25 ml of 5% aqueous sodium hydroxide, once with 25 ml water, twice with 25 ml 1N hydrochloric acid, and once with 25 ml water. The methylene chloride solution was dried over anhydrous potassium carbonate and evaporated to yield the amide.

2-Benzoyl-1,2,3,4-tetrahydroisoquinoline (58). The above procedure with 37 and benzoyl chloride gave 3.2 g (93%) of 58 as a yellow oil;[84] ir (#12720, film) 3050 (m), 2960 (m), 1660 (s), 1450 (s), 1280 (s), 1160 (m), 1130 (m), 1060 (m), 1000 (m), 945 (m), 840 (w), 800 (m), 750 (b); nmr (#15204, $DCCl_3$) δ 7.30 (s, 5H), 7.06 (s, 4H), 4.67 (s, 2H), 3.67 (m, 2H), 2.80 (m, 2H).

2-(4'-Nitrophenacetyl)-1,2,3,4-tetrahydroisoquinoline (59). The above procedure with 37 and p-nitrophenacetyl chloride gave 2.4 g (55%) of 59 as a yellow solid, mp 139-140° (isopropanol); ir (#12736, KBr) Appendix, A-18; nmr (#15295, $DCCl_3$) Appendix, B-12.

Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.87; H, 5.44; N, 9.45.

2-(4'-Nitrophenacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (60). The above procedure with 46 and p-nitrophenacetyl chloride gave 4.2 g (79%) of 60 as a tan solid, mp 92-94° (ethyl acetate-diethyl ether); ir (#12737, KBr)

Appendix, A-19; nmr (#15296, $DCCl_3$) Appendix, B-13.

Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.65; N, 7.86. Found: C, 64.14; H, 5.74; N, 8.22.

Preparation of 2-[β-(4'-Nitrophenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (45). Compound 45 was prepared by the method of Brown.[39] A solution of 1.9 g (13 mmol) of boron trifluoride etherate in 15 ml of tetrahydrofuran was added dropwise over a period of 0.5 hr to a stirred slurry of 1.5 g (5 mmol) of 2-(4'-nitrophenylacetyl)-1,2,3,4-tetrahydroisoquinoline (59) and 0.38 g (10 mmol) of sodium borohydride in 40 ml of tetrahydrofuran at 0-5° under a nitrogen atmosphere. The slurry was then heated under reflux for 1.5 hr and, after cooling, the excess borane was decomposed with 10% hydrochloric acid. The solution was concentrated, and the residue was partitioned between 50 ml of ether and 100 ml of water. The ether layer was dried over potassium carbonate and then hydrogen chloride gas was bubbled into the solution. The resulting salt was collected by filtration and recrystallized from ethanol to yield 1.1 g (69%) of 45·HCl as yellow needles, mp 252-256°d.

The base was prepared by dissolving the salt in water and making the aqueous solution basic with a saturated solution of sodium bicarbonate. The resulting solid was collected by filtration and recrystallized from ethanol to give 45, mp 105-107°; uv max (#1036, CH_3OH) base 271 nm (ε11,200), (#872, CH_3OH) hydrochloride 264 nm (ε10,900); ir (#12967, KBr) Appendix, A-20; nmr (#16030, $DCCl_3$) Appendix, B-14.

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.00; H, 6.41; N, 9.73.

Preparation of 2-[β-(4'-Nitrophenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (52). Compound 52 was prepared from 60 by the method of Brown[39] as described above. The hydrochloride, mp 228-230°d (isopropanol), was obtained in 40% yield. The base was prepared as above and was recrystallized from ethanol to give 52, mp 119-120°; uv max (#1034, CH_3OH) base 280 nm (ϵ14,100), (#871, CH_3OH) hydrochloride 273 nm (ϵ12,100); ir (#12980, KBr) Appendix, A-21; nmr (#16051, $DCCl_3$) Appendix, B-15.

Anal. Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.69; H, 6.54; N, 8.29.

Preparation of α,α-Dideutero-2-benzyl-1,2,3,4-tetrahydroisoquinolinium Hydrochloride (61). A slurry of 0.47 g (2.0 mmol) of 2-benzoyl-1,2,3,4-tetrahydroisoquinoline and 0.10 g (2.4 mmol) of lithium aluminum deuteride in 40 ml of anhydrous diethylether were heated under reflux overnight. The excess lithium aluminum deuteride was decomposed with water, the mixture was filtered, and the filtrate was dried over anhydrous potassium carbonate. Hydrogen chloride gas was bubbled through the ether solution, and the resulting oil crystallized to a white solid when triturated with an ethanol-ether mixture. A yield of 0.4 g (77%) of 61, mp 204-206°, was obtained; ir (#12753, KBr) hydrochloride Appendix, A-22; nmr (#15317, D_2O) Appendix, B-16.

Preparation of 2,6-Dichlorobenzylhexamethylenetetraminium Chloride (62). A solution of 67.2 g (0.34 mol) of 2,6-dichlorobenzyl bromide and 52.0 g (0.37 mol) of hexamethylenetetramine in 400 ml of chloroform was allowed to stand at ambient temperature for 24 hr. The white solid which precipitated was collected by filtration and dried to yield 100 g (89%) of 62, mp 203°d (ethanol); ir (#13326, KBr) 1600 (b), 1580 (m), 1460 (s), 1440 (s), 1270 (s), 1215 (m), 1110 (s), 1040 (s), 1000 (s), 935 (s), 825 (s), 800 (b), 730 (m).

Preparation of p-Nitrobenzylhexamethylenetetraminium Bromide (63). Hexamethylenetetramine (27.6 g, 0.2 mol) and p-nitrobenzyl bromide (43.2 g, 0.2 mol) were dissolved in 500 ml of acetone and 50 ml of ethanol and the solution was heated under reflux for 1 hr. After cooling the solution, a solid precipitated and the resulting pale yellow solid was collected by filtration, washed with acetone and dried to yield 68.6 g (97%) of 63, mp 176-177°d, lit.[85] mp 168°; ir (#12957, KBr) 1600 (m), 1520 (s), 1370 (s), 1280 (s), 1120 (m), 1050 (s), 1020 (b), 945 (m), 900 (m), 860 (s), 820 (b), 785 (s), 755 (s), 705 (b).

Preparation of 1,3,5-Tris(p-nitrobenzyl)hexahydro-s-triazine (64). Compound 64 was prepared according to the procedure of Graymore.[86] p-Nitrobenzylhexamethylenetetraminium bromide (60 g, 0.17 mol) was dissolved in 300 ml of water and 60 ml of concentrated ammonium hydroxide and the solution was heated under reflux for 1.5 hr. The solution was cooled and

the orange-brown solid which precipitated was collected by filtration and dried. The solid was then ground and recrystallized from benzene to yield 25.2 g (90%) of 64 as tan needles, mp 158-159°, lit.[86] mp 158°; ir (#12944, KBr) 1600 (m), 1520 (s), 1360 (s), 1180 (m), 1010 (m), 925 (s), 850 (m), 740 (m); nmr (#15659, $DCCl_3$) δ 7.79 (AB, J_{AB} = 8.5 Hz, $\Delta\nu_{AB}$ = 35.5 Hz, 12H), 3.83 (s, 6H), 3.50 (s, 6H).

Preparation of 2,6-Dichlorobenzylamine Hydrochloride (65). Compound 65 was prepared by the procedure of Morley.[87] A mixture of 67.0 g (0.2 mol) of 2,6-dichlorobenzylhexamethylenetetraminium chloride in 150 ml of 6N hydrochloric acid was subjected to steam distillation. After 1 l. of distillate was collected, the pot residue was concentrated to yield a white solid. This solid was recrystallized from ethanol to give 23.0 g (54%) of 65, mp 256-258, lit.[87] mp 237-238°; ir (#13419, KBr) 3000 (b), 1560 (b), 1490 (s), 1415 (m), 1200 (m), 1160 (m), 890 (b), 775 (s); nmr (#966, D_2O) δ 7.60 (m, 3H), 4.15 (s, 2H).

Preparation of p-Nitrobenzylamine Hydrochloride (66). Compound 66 was prepared according to the procedure of Graymore.[86] 1,3,5-Tris(p-nitrobenzyl)hexahydro-s-triazine (24.0 g, 4.9 mmol) was dissolved in 350 ml of water and 40 ml of concentrated hydrochloric acid. Steam distillation (1 l. of distillate) removed most of the formaldehyde, and the solution on concentration gave a yellow solid. This solid was recrystallized from water to yield 19.7 g (72%) of p-nitrobenzylamine hydrochloride, mp 267-269°d, lit.[86] mp 256°;

ir (#12868, KBr) 3000 (b), 1600 (s), 1530 (s), 1350 (s), 1100 (s), 1020 (w), 910 (m), 860 (s), 785 (w), 750 (s), 740 (s), 700 (s); nmr (#15814, D_2O) δ 7.83 (AB, J_{AB} = 9.0 Hz, $\Delta\nu_{AB}$ = 32.0 Hz, 4H), 4.27 (s, 2H).

Preparation of p-Nitrophenylacetamide (67). p-Nitrophenylacetic acid (18.1 g, 0.1 mol) was heated under reflux in 75 ml of thionyl chloride for 1.5 hr. The excess thionyl chloride was removed by distillation under reduced pressure and the acid chloride was then added in portions to a stirred solution of 150 ml of cold concentrated ammonium hydroxide. The resulting solid was collected by filtration, washed with water and recrystallized from acetonitrile to yield 15.7 g (87%) of 67 as tan needles, mp 197-199°, lit.[88] mp 196-197.5°; ir (#12870, KBr) 3600 (s), 1670 (s), 1550 (s), 1430 (m), 1360 (s), 1120 (w), 885 (m), 825 (m), 750 (m), 720 (s); nmr (#15827, d_6-DMSO) δ 7.72 (AB, J_{AB} = 8.5 Hz, $\Delta\nu_{AB}$ = 38.0 Hz, 4H), 3.41 (s, 2H).

Preparation of β-(4-Nitrophenyl)ethylamine Hydrochloride (68). Compound 68 was prepared by the method of Brown.[39] To a slurry of 14.4 g (0.08 mol) of p-nitrophenylacetamide in 100 ml of tetrahydrofuran was added 200 ml 1M borane in tetrahydrofuran dropwise under a nitrogen atmosphere at ice bath temperature over a 0.5 hr period. The stirred mixture was heated under reflux overnight, and the excess borane was decomposed with 10% aqueous hydrochloric acid. The solution was made basic with 10% aqueous sodium hydroxide and concentrated, and the residue was partitioned between 200 ml

of water and 100 ml of diethylether. The aqueous layer was washed twice with 50 ml of ether and the combined ether extracts were dried over barium oxide. After filtration, the ether solution was treated with hydrogen chloride gas and the salt which precipitated was collected by filtration and recrystallized from ethanol to yield 10.7 g (73%) of 68 as pale yellow needles, mp 213-215°, lit.[89] mp 209-210°; ir (#12975, KBr) 3000 (b), 1530 (s), 1350 (s), 1250 (m), 1110 (m), 960 (m), 885 (m), 860 (m), 825 (m), 750 (s); nmr (#16053, D_2O) δ 7.55 (AB, J_{AB} = 8.5 Hz, $\Delta\nu_{AB}$ = 30.0 Hz, 4H), 3.15 (m, 4H).

General Procedure for the Preparation of 3,4-Dihydro-1,3,2H-benzoxazines. To a solution of 0.10 g (0.0018 mol) of potassium hydroxide in 5 ml of methanol was added 6.6 g (0.066 mol) of 91% paraformaldehyde and the mixture was warmed to effect solution. After cooling the solution in an ice bath, 0.10 mol of a phenol dissolved in 10 ml of methanol and 0.10 mol of an amine dissolved in 10 ml of methanol were added. The stirred mixture was heated under reflux under nitrogen for 1 hr. The solution was evaporated and the residue was dissolved in 200 ml of methylene chloride. The organic layer was washed with 100 ml of water, twice with 50 ml of 5% aqueous sodium hydroxide and finally with 100 ml of water. After drying the methylene chloride solution over anhydrous magnesium sulfate, the solution was evaporated to yield an oil which slowly crystallized on standing. The solid was then recrystallized and all analytical, physical and spectral data were obtained.

3,4-Dihydro-3-benzyl-6-methoxy-1,3,2H-benzoxazine (70). The above procedure using p-methoxyphenol and benzylamine gave 10.5 g (41%) of 70 as a white crystalline solid, mp 73-75° (hexane), lit.[18] mp 74-75°; uv max (#1030, CH_3OH) 293 nm (ε3700); ir (#12866, KBr) 2950 (w), 1500 (s), 1440 (m), 1280 (s), 950 (s), 880 (m), 840 (m), 810 (s), 770 (m), 745 (b), 700 (b); nmr (#15731, $DCCl_3$) δ 7.22 (s, 5H), 6.67 (m, 2H), 6.38 (m, 1H), 4.71 (s, 2H), 3.82 (s, 4H), 3.60 (s, 3H).

3,4-Dihydro-3-(β-phenethyl)-6-methoxy-1,3,2H-benzoxazine (72). The above procedure using p-methoxyphenol and β-phenethylamine gave 17.0 g (63%) of 72 as a white solid, mp 72-74° (ethanol), lit.[18] mp 73-74°; uv max (#1031, CH_3OH) 293 nm (ε3600); ir (#12869, KBr) 2950 (m), 1600 (w), 1500 (s), 1470 (m), 1340 (m), 1315 (m), 1270 (m), 1200 (s), 1140 (s), 1050 (s), 975 (w), 945 (s), 920 (s), 890 (s), 865 (s), 820 (s), 755 (b), 705 (b); nmr (#15730, $DCCl_3$) δ 7.14 (s, 5H), 6.63 (d, 2H), 6.42 (m, 1H), 4.76 (s, 2H), 3.93 (s, 2H), 3.67 (s, 3H), 2.90 (m, 4H).

3,4-Dihydro-3-(4'-nitrobenzyl)-6-methoxy-1,3,2H-benzoxazine (71). The above procedure using p-methoxyphenol and p-nitrobenzylamine gave 11.6 g (39%) of 71 as pale yellow needles, mp 90-92° (methanol); uv max (#1032, CH_3OH) 270 nm (ε10,700); ir (#12872, KBr) Appendix, A-23; nmr (#15734, $DCCl_3$) Appendix, B-17.

Anal. Calcd for $C_{16}H_6N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.88, H, 5.32, N, 9.40.

3,4-Dihydro-3-[β-(4'-nitrophenyl)ethyl]-6-methoxy-1,3,2H-benzoxazine (73). The above procedure using p-methoxyphenol and β-(p-nitrophenyl)ethylamine gave 20.4 g (65%) of 73 as pale yellow crystals, mp 85-86° (methanol); uv max (#1033, CH_3OH) 279 nm (ϵ11,800); ir (#13190, KBr) Appendix, A-24; nmr (#652, $DCCl_3$) Appendix, B-18.

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.95; H, 5.77; N, 8.91. Found: C, 64.90; H, 5.76; N, 9.26.

3,4-Dihydro-3-(2',6'-dichlorobenzyl)-6-methoxy-1,3,2H-benzoxazine (74). The above procedure using p-methoxyphenol and 2,6-dichlorobenzylamine gave 4.7 g (36%) of 74 as a white solid, mp 137-139° (acetonitrile); uv max (#1041, CH_3OH) 291 nm (ϵ2800); ir (#13422, KBr) Appendix, A-25; nmr (#976, d_6-DMSO) Appendix, B-19.

Anal. Calcd for $C_{16}H_{15}Cl_2NO_2$: C, 59.27; H, 4.66; N, 4.32. Found: C, 59.33; H, 4.58; N, 4.68.

3,4-Dihydro-3-benzyl-6-methyl-1,3,2H-benzoxazine (75). The above procedure using p-methylphenol and benzylamine gave 12.9 g (54%) of 75 as a white solid, mp 70-72° (methanol), lit.[18] mp 71-72°; ir (#12936, KBr) 2950 (w), 1500 (s), 1330 (m), 1225 (m), 1020 (w), 1000 (m), 950 (s), 920 (m), 875 (w), 830 (s), 740 (s), 700 (b); nmr (#15834, $DCCl_3$) δ 7.23 (s, 5H), 6.70 (m, 3H), 4.75 (s, 2H), 3.83 (s, 4H), 2.20 (s, 3H).

Preparation of 3,4-Dihydro-3-methyl-6-methoxy-1,3,2H-benzoxazine (69). To a cold solution of 18.5 g (0.23 mol) of

37% aqueous formaldehyde was added 12.4 g (0.10 mol) of 4-methoxyphenol dissolved in 40 ml of ethanol and then 10.5 g (0.1 mol) of 30% aqueous methylamine. The stirred solution was heated under reflux under a nitrogen atmosphere for 2 hr. After cooling, the solution was partitioned between 200 ml of methylene chloride and 200 ml of water. The organic layer was washed three times with 100 ml of 5% aqueous sodium hydroxide and once with 100 ml of water, dried over anhydrous magnesium sulfate, and evaporated to yield a tan oil. The residual oil was chromatographed on 50 g of basic alumina and eluted with hexane. The resulting oil solidified to a white solid when stored in the cold overnight. The solid was recrystallized from pentane to yield 7.8 g (44%) of 69, mp 41-43°; uv max (#1029, CH_3OH) 290 nm (ϵ3400); ir (#12949, KBr) Appendix, A-26; nmr (#16002, $DCCl_3$) Appendix B-20.

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.19; H, 7.34; N, 8.02.

Preparation of 3,4-Dihydro-3-benzyl-3,6-dimethyl-1,3,2H-benzoxazinium Iodide (78). A solution of 1.2 g (0.005 mol) of 3,4-dihydro-3-benzyl-6-methyl-1,3,2H-benzoxazine (75) in 5 ml of methyl iodide was allowed to stand at ambient temperature for 24 hr. During this time a white solid precipitated, and this solid was recrystallized from isopropanol to yield 1.9 g (100%) of 78, mp 181-183°d; ir (#12940, KBr) Appendix, A-27; nmr (#273, d_6-DMSO) Appendix, B-21.

Anal. Calcd for $C_{17}H_{20}INO$: C, 53.55; H, 5.29; N, 3.67. Found: C, 53.45; H, 5.27; N, 3.91.

Preparation of 3,4-Dihydro-3,4-dibenzyl-6-methyl-1,3,2H-benzoxazinium Bromide (79). A mixture of 1.2 g (0.005 mol) of 3,4-dihydro-3-benzyl-6-methyl-1,3,2H-benzoxazine (75) and 1.7 g (0.001 mol) of benzyl bromide was heated under a nitrogen atmosphere at 85° for 2 hr. The resulting yellow glass was triturated with ethyl acetate, and a white solid precipitated which was recrystallized from ethanol-ethyl acetate-ether to yield 1.5 g (75%) of 79 as white crystals, mp 154°; ir (#12939, KBr) Appendix, A-28; nmr (#275, $DCCl_3$) Appendix, B-22.

Anal. Calcd for $C_{23}H_{20}BrNO \cdot 0.50\ H_2O$: C, 65.87; H, 6.01; N, 3.34. Found: C, 65.67; H, 5.78; N, 3.60.

Preparation of 2-(Benzylaminomethyl)-4-methylphenol (77). A solution of 7.2 g (0.03 mol) of 3,4-dihydro-3-benzyl-6-methyl-1,3,2H-benzoxazine (75) in 50 ml of ethanol was treated with 15 ml of concentrated hydrochloric acid, and the solution was allowed to stand at ambient temperature overnight. The solution was concentrated and the residue was partitioned between 100 ml of methylene chloride and 100 ml of saturated aqueous sodium bicarbonate. After separation, the organic layer was washed with water, dried over anhydrous potassium carbonate, and evaporated to yield an oil which crystallized to a white solid on cooling. The solid was recrystallized from pentane to yield 5.0 g (73%) of 77 as white needles, mp 30-32°; ir (#12943, KBr) 2900 (b), 1500 (s), 1260 (s), 1090 (w), 820 (s), 750 (b), 700 (s); nmr (#15958, $DCCl_3$) Appendix, B-23. This solid was used without further

purification. The product was analyzed as the hydrobromide, mp 184° (isopropanol-ether); ir (#12945, KBr) Appendix, A-29.

Anal. Calcd for $C_{15}H_{18}BrNO$: C, 58.45; H, 5.89; N, 4.55. Found: C, 58.19; H, 5.65; N, 4.73.

Preparation of 3,4-Dihydro-2-p-Chlorophenyl-3-benzyl-6-methyl-1,3,2H-benzoxazine (76). A solution of 2.3 g (0.01 mol) of 2-benzylaminomethyl-4-methylphenol (77) and 1.4 g (0.01 mol) of p-chlorobenzaldehyde in 25 ml of benzene was heated under reflux for 24 hr utilizing a Dean-Stark apparatus to remove water. The benzene solution was then concentrated and the residual brown oil crystallized to a tan solid after cooling for three days. The solid was recrystallized from isopropanol to yield 2.3 g (66%) of 76 as a white solid, mp 76-78°; ir (#12950, KBr) Appendix, A-30; nmr (#383, $DCCl_3$) Appendix, B-24.

Anal. Calcd for $C_{22}H_{20}ClNO$: C, 75.52; H, 5.76; N, 4.00. Found: C, 75.61; H, 5.92; N, 4.24.

General Procedure for the Preparation of the [4H]-1-Oxa-3-azonia-2-boratanaphthalenes.[96] To an ice cold solution of 0.005 mol of the appropriate 3,4-dihydro-1,3,2H-benzoxazine in 10 ml of tetrahydrofuran was added 6 ml of 1M borane in tetrahydrofuran, and the solution was stirred at ice bath temperatures for 0.5 hr. The solvent was then evaporated to yield a white solid. An nmr spectrum of this solid was recorded. The solid was then heated, neat, under a nitrogen atmosphere at 200° for 20 min. On cooling, a white solid crystallized, and this solid was recrystallized from cyclohexane-

benzene to yield the corresponding [4H]-1-oxa-3-azonia-2-boratanaphthalene. All analytical and spectral data were then obtained.

3,3-Dimethyl-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (85). The above procedure using 69 gave 1.3 g (68%) of 85, mp 133-135°d; ir (#12958, KBr) Appendix, A-31; nmr (#395, $DCCl_3$) Appendix, B-25.

Anal. Calcd for $C_{10}H_{16}BNO_2$: C, 62.21; H, 8.36; N, 7.26. Found: C, 62.46; H, 8.06; N, 7.13.

3-Benzyl-3-methyl-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (86). The above procedure using 70 gave 0.7 g (53%) of 86, mp 141-144°; ir (#12937, KBr) Appendix, A-32; nmr (#396, $DCCl_3$) Appendix, B-26.

Anal. Calcd for $C_{16}H_{20}BNO_2$: C, 71.40; H, 7.49; N, 5.21. Found: C, 71.00; H, 7.33; N, 5.34.

3-Methyl-3-(β-phenethyl)-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (87). The above procedure using 72 gave 1.1 g (78%) of 87, mp 103-110°d; ir (#13166, KBr) Appendix, A-33; nmr (#624, $DCCl_3$) Appendix, B-27.

Anal. Calcd for $C_{17}H_{22}BNO_2$: C, 72.10; H, 7.83; N, 4.95. Found: C, 71.70; H, 7.62; N, 5.22.

3-Benzyl-3,6-dimethyl[4H]-1-oxa-3-azonia-2-boratanaphthalene (88). The above procedure using 75 gave 0.7 g (54%) of 88, mp 159-161°; ir (#12942, KBr) Appendix, A-34; nmr (#276, $DCCl_3$) Appendix, B-28.

Anal. Calcd for $C_{16}H_{20}BNO$: C, 75.91; H, 7.96; N, 5.53. Found: C, 75.95; H, 7.91; N, 5.53.

Attempted Preparation of 3-Benzyl-3-p-chlorobenzyl-6-methyl[4H]-1-oxa-3-azonia-2-boratanaphthalene (89). To an ice cold solution of 1.2 g (0.005 mol) of 3,4-dihydro-2-p-chlorophenyl-3-benzyl-6-methyl-1,3,2H-benzoxazine (76) in 10 ml of the tetrahydrofuran was added 6 ml of 1M borane in tetrahydrofuran, and the solution was stirred at ice bath temperatures for 1 hr. A white solid, mp 196°, precipitated from the solution during this time. The infrared spectrum (#12965) of this compound showed a B-H stretching adsorption at 2400 cm^{-1}.

The white solid was heated, neat, at 220° for 20 min under a nitrogen atmosphere. The resulting solid was not the expected product of rearrangement but was shown by its chemical, physical and spectral properties to be 2-(benzyl-p-chlorobenzylaminomethyl)-4-methylphenol (90), mp 56-58° (pentane); ir (#12974, KBr) Appendix, A-35; nmr (#374, $DCCl_3$) Appendix, B-29.

Anal. Calcd for $C_{22}H_{22}ClNO$: C, 75.09; H, 6.30; N, 3.98. Found: C, 75.31; H, 6.28; N, 4.12.

Preparation of 2-(Benzylmethylaminomethyl)-4-methoxyphenol (91). A mixture of 0.30 g (1.1 mmol) of 3-benzyl-3-methyl-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (86) in 20 ml of 10% aqueous hydrochloric acid was heated under reflux until all the solid had dissolved. The solution was allowed to stand overnight at ambient temperature, and then

was made basic with a saturated solution of sodium bicarbonate. The basic solution was extracted three times with 25 ml of ether. The combined ether extracts were dried over anhydrous sodium sulfate and evaporated to yield 0.25 g (89%) of 91 as a yellow oil; ir (#12956, film) Appendix, A-36; nmr (#16019, $DCCl_3$) Appendix, B-30. The product was analyzed as the hydrobromide, mp 183-184° (isopropanol).

Anal. Calcd for $C_{16}H_{20}BrNO_2$: C, 56.81; H, 5.96; N, 4.14. Found: C, 56.67; H, 5.98; N, 4.36.

Preparation of 6,12-Epoxy-6H,12H-dibenzo[b,f]-1,5-dioxacin (98). Following the procedure of Adams,[44] 30.0 g (0.25 mol) of salicylaldehyde and 25 g (0.41 mol) of acetic anhydride were mixed and cooled to 0° in an ice-salt bath. One drop of concentrated sulfuric acid was added and the mixture was vigorously stirred. After 15 min, the white solid which precipitated was collected by filtration and washed with water. This solid was recrystallized from ethanol to yield 20.0 g (71%) of 98 as white needles, mp 127-130°, lit.[44] mp 130°; ir (#13253, KBr) 1750 (m), 1605 (m), 1590 (m), 1500 (s), 1480 (m), 1330 (m), 1230 (s), 1120 (m), 1080 (m), 1050 (m), 960 (b), 810 (m), 765 (b); nmr (#737, $DCCl_3$) δ 7.28-6.80 (m, 8H), 6.40 (s, 2H).

Preparation of 6,12-(Carbethoxyimino)-6H,12H-dibenzo [b,f]-1,5-dioxacin (99). Compound 99 was prepared according to the procedure of Merten and Muller.[45] A mixture of 12.2 g (0.1 mol) of salicylaldehyde, 4.5 g (0.05 mol) of ethylcarbamate, and 2 ml of boron trifluoride-diethyl etherate in 50 ml

of benzene was heated under reflux overnight utilizing a Dean-Stark apparatus. The benzene solution was diluted with 50 ml more of benzene and washed three times with 30 ml of 5% sodium hydroxide solution and once with 100 ml of water. The benzene layer was dried over potassium carbonate and concentrated to leave a white solid as residue. This solid was recrystallized from ethanol to yield 9.0 g (60%) of 99 as a white solid, mp 153-154°, lit.[45] mp 154°; ir (#13246, KBr) 3000 (w), 1715 (s), 1600 (m), 1590 (m), 1500 (s), 1440 (s), 1340 (s), 1270 (s), 1120 (m), 1040 (s), 970 (b), 800 (m), 760 (b); nmr (#673, $DCCl_3$) δ 7.56-6.60 (m, 10H), 4.26 (q, J = 9 Hz, 2H), 1.27 (t, J = 9 Hz, 3H).

Preparation of 6,12-(Carbobenzyloxyimino)-6H,12H-dibenzo[b,f]-1,5-dioxacin (100). Starting from benzylcarbamate (157), the above procedure gave 11.2 g (62%) of 100 as a brown oil. This oil was used without further purification or characterization; ir (#13250, film) 3050 (m), 2950 (m), 1710 (b), 1510 (s), 1490 (s), 1100 (b), 800 (s), 750 (b); nmr (#736, $DCCl_3$) δ 7.30 (s, 5H), 7.30-6.70 (m, 10H), 5.16 (s, 2H).

Attempted Preparation of 6,12-(Benzoylimino)-6H,12H-dibenzo[b,f]-1,5-dioxacin (101). Starting from benzamide, the above procedure gave 6.8 g of a white solid (105), mp 212-213°d (acetonitrile) of undetermined structure and not the expected 101; ir (#13429, KBr) Appendix, A-37; nmr (#725, d_6-acetone) δ 8.32-7.00 (m).

Anal. Calcd for $C_{21}H_{15}NO_3$: C, 76.58; H, 4.59; N, 4.25. Found: C, 67.99; H, 4.11; N, 6.20.

Attempted Preparation of 6,12-Imino-6H,12H-dibenzo-[b,f]-1,5-dioxacin (102). A mixture of 11.2 g (0.31 mol) of 6,12-(carbobenzyloxyimino)-6H,12H-dibenzo[b,f]-1,5-dioxacin (100) and 1.5 g of 10% palladium on charcoal in 200 ml of ethanol was hydrogenated at 10 psi for 3 hr. The mixture was filtered and the filtrate concentrated to leave a pale yellow solid as residue. This solid was recrystallized from ethanol to yield 3.8 g (55%) of a compound, mp 171-173°, which was assigned the structure bis-(o-hydroxybenzyl)amine (104), lit.[90] mp 170-171°, by its physical and spectral data; ir (#13261, KBr) 3000-2400 (b), 1690 (s), 1480 (b), 1250 (b), 880 (w), 755 (s); nmr (#747, d_6-acetone) δ 7.26-6.68 (m, 11H), 3.88 (s, 4H).

Preparation of 1-Cyano-2-benzoyl-1,2-dihydroisoquinoline (108). This compound was prepared by the method of Popp and Blount.[51] To a vigorously stirred mixture of 25.8 g (0.2 mol) of isoquinoline, 250 ml of methylene chloride, 39.0 g (0.6 mol) of potassium cyanide and 100 ml of water in a one l. Morton flask was added 56.2 g (0.4 mol) of benzoyl chloride dropwise over a 3 hr period. After stirring for an additional 0.5 hr, the methylene chloride layer was separated and washed twice with 50 ml of water, four times with 50 ml of 10% hydrochloric acid, once with 50 ml of water, four times with 50 ml of 5% sodium hydroxide and finally twice with 50 ml of water. The resulting yellow, methylene chloride solution was dried over anhydrous magnesium sulfate, filtered and concentrated to yield a yellow oil. This oil solidified

on standing to give a white solid. One recrystallization of the solid from absolute ethanol yielded 39.8 g (77%) of 108 as white needles, mp 126-128°, lit.[51] mp 124-125°; ir (#12141, KBr) 1680 (s), 1650 (s), 1590 (m), 1490 (w), 1460 (m), 1400 (w), 1355 (s), 1245 (m), 1065 (m), 1010 (w), 950 (m), 900 (m), 875 (m), 785 (b), 755 (w), 735 (b); nmr (#5610, $DCCl_3$) δ 7.72-7.20 (m, 9H), 6.58 (s, 1H), 6.34 (AB, J_{AB} = 7.5 Hz, $\Delta\nu_{AB}$ = 33.7 Hz, 2H).

General Procedure for the Preparation of Substituted 1-Benzylisoquinolines. These compounds were prepared by the method of Popp and Wefer[52a,b] and Uff and Kershaw.[52c,d] A solution of 0.09 mol of substituted benzyl bromide in 100 ml of dimethylformamide was added dropwise to a mechanically-stirred, cooled slurry of 23.4 g (0.09 mol) of 1-cyano-2-benzyl-1,2-dihydroisoquinoline and 4.3 g (0.10 mol) of 56% sodium hydride in oil in 200 ml of dimethylformamide. The reaction mixture was stirred at 0-5° under a nitrogen atmosphere for 3 hr after the addition was complete. The excess sodium hydride was then decomposed with ethanol, and the solution was concentrated.

A mixture of 400 ml of ethanol and 100 ml of 10% sodium hydroxide was added and the solution was heated under reflux for 2 hr. The mixture was concentrated, and 300 ml of water and 300 ml of chloroform were added. The layers were separated, and the washed chloroform layer was dried over anhydrous magnesium sulfate, filtered, and concentrated to yield the product as an oil.

1-Benzylisoquinoline (109). The reaction of 108 with benzyl bromide gave 17.7 g (90%) of 109 as a yellow oil which was converted to the picrate derivative, mp 182-184° (ethanol), lit.[52d] mp 182-184°; ir (#12151, film) 3050 (m), 2950 (w), 1620 (m), 1590 (m), 1560 (s), 1490 (s), 1380 (s), 1150 (w), 1040 (m), 1030 (m), 875 (m), 805 (m), 755 (b), 720 (b), 705 (b); nmr (#10685, $DCCl_3$) δ 8.53 (d, J = 6.0 Hz, 1H), 8.17-6.84 (m, 10H), 4.50 (s, 2H).

1-(3',4'-Dimethoxybenzyl)isoquinoline (110). The reaction of 108 with 21 gave 19.9 g (79%) of orange oil which solidified upon stirring in hexane at ice bath temperatures. The solid was recrystallized from pentane-ethyl ether to give 110 as white crystals, mp 76-77°, lit.[52d] mp 73-74°, which were converted to the picrate, mp 165-166° (ethanol), lit.[52d] mp 165-165.5°. The ir and nmr spectra were identical to those obtained from an authentic sample of 110;[90] ir (#12206, KBr) 2950 (w), 1550 (w), 1500 (s), 1240 (s), 1150 (s), 1030 (s), 945 (w), 840 (s), 800 (b), 760 (w), 740 (m); nmr (#12055, $DCCl_3$) δ 8.30-6.99 (m, 6H), 6.70-6.50 (m, 3H), 4.46 (s, 2H), 3.67 (s, 6H).

1-(3',4'-Methylenedioxy)isoquinoline (111). The reaction of 108 with 22 gave 17.3 g (73%) of orange oil which solidified on stirring in hexane at ice bath temperatures. The solid was recrystallized from pentane-ethyl ether to give 111 as white crystals, mp 78-80°, lit.[52d] mp 80-81° which were converted to the picrate, mp 186-189°d (ethanol), lit.[52d] mp 179°d. The ir and nmr spectra were

identical to those obtained from an authentic sample of 111,[90] ir (#12228, KBr) 1600 (w), 1490 (s), 1435 (s), 1355 (m), 1240 (s), 1180 (m), 1095 (w), 1030 (s), 935 (s), 880 (m), 815 (b), 740 (b); nmr (#11131, $DCCl_3$) δ 8.48 (d, 1H), 8.25-7.23 (m, 5H), 6.68 (s, 3H), 5.74 (s, 2H), 4.55 (s, 2H).

Preparation of 1-(3',4'-Dimethoxybenzyl)-2-methylisoquinolinium Iodide (112). A mixture of 2.5 g (9.0 mmol) of 1-(3',4'-dimethoxybenzyl)isoquinoline (110) in 30 ml of iodomethane was converted quantitatively to the quaternary salt by heating the solution under reflux under a nitrogen atmosphere for 3 hr. The excess iodomethane was removed by distillation and the yellow solid, mp 199-202°d, which had formed was removed by filtration, washed with ether and dried. No further purification was necessary; ir (#12213, KBr) Appendix, A-38; nmr (#10374, $DCCl_3$) Appendix, B-31.

Anal. Calcd for $C_{19}H_{20}INO_2$: C, 54.17; H, 4.79; N, 3.33. Found: C, 53.92; H, 4.65; N, 3.23.

Preparation of 1-(3',4'-Methylenedioxybenzyl)-2-methylisoquinolinium Iodide (113). 1-(3',4'-Methylenedioxybenzyl)isoquinoline (111) was converted quantitatively to the methiodide, mp 231-234°d, as described above; ir (#12227, KBr) Appendix, A-39; nmr (#16196, d_6-DMSO) Appendix, B-32.

Anal. Calcd for $C_{18}H_{16}INO_2$: C, 53.35; H, 3.98; N, 3.46. Found: C, 53.61; H, 3.89; N, 3.74.

General Procedure for the Preparation of Salts of Substituted 1-Benzylisoquinolines. A mixture of 0.010 mol of the substituted 1-benzylisoquinoline and 0.015 mol of the substituted benzyl bromide in 30 ml of tetrahydrofuran was heated under reflux for 48 hr. After cooling, the resulting solid was collected by filtration, washed with ether, and dried. The salt was recrystallized and all spectral and analytical data were then obtained.

1,2-Dibenzylisoquinolinium Bromide (114). The above procedure with 109 and benzyl bromide gave 2.6 g (67%) of 114 as white needles, mp 204-206° (isopropanol); ir (#13085, KBr) Appendix, A-40; nmr (#16211, d_6-DMSO) Appendix, B-33.

Anal. Calcd for $C_{23}H_{20}BrN$: C, 70.77; H, 5.16; N, 3.59. Found: C, 70.42; H, 5.15; N, 3.71.

1-(3',4'-Dimethoxybenzyl)-2-benzylisoquinolinium Bromide (115). The above procedure with 110 and benzyl bromide gave 3.2 g (71%) of 115 as yellow needles, mp 189-191° (isopropanol-ethyl ether); ir (#11467, KBr) Appendix, A-41; nmr (#12108, $DCCl_3$) Appendix, B-34.

Anal. Calcd for $C_{25}H_{24}BrNO_2$: C, 66.67; H, 5.37; N, 3.11. Found: C, 66.85; H, 5.45; N, 2.98.

1-(3',4'-Dimethoxybenzyl)-2-(4"-nitrobenzyl)isoquinolinium Bromide (116). The above procedure with 110 and p-nitrobenzyl bromide gave 4.5 g (91%) of 116 as a yellow solid, mp 193-195°d (ethanol); ir (#13084, KBr) Appendix, A-42; nmr (#16168, d_6-DMSO) Appendix, B-35.

Anal. Calcd for $C_{25}H_{23}BrN_2O_4$: C, 60.61; H, 4.68; N, 5.66. Found: C, 60.71; H, 4.75; N, 5.90.

1-(3',4'-Dimethoxybenzyl)-2-(2",6"-dichlorobenzyl)-isoquinolinium Bromide (117). The above procedure with 110 and 2,6-dichlorobenzyl bromide gave 3.6 g (60%) of 117 as yellow needles, mp 172-174°d (isopropanol); ir (#13421, KBr) Appendix, A-43; nmr (#975, $DCCl_3$) Appendix, B-36.

Anal. Calcd for $C_{25}H_{22}BrCl_2NO_2$: C, 57.82; H, 4.27; N, 2.70. Found: C, 58.16; H, 4.00; N, 2.87.

1-(3',4'-Methylenedioxybenzyl)-2-benzylisoquinolinium Bromide (118). The above procedure with 111 and benzyl bromide gave 3.2 g (74%) of 118 as a yellow solid, mp 220-225°d (ethanol); ir (#13091, KBr) Appendix, A-44; nmr (#16277, d_6-DMSO) Appendix, B-37.

Anal. Calcd for $C_{24}H_{20}BrNO_2$: C, 66.36; H, 4.64; N, 3.23. Found: C, 66.45; H, 4.58; N, 3.41.

1-(3',4'-Methylenedioxybenzyl)-2-(4"-nitrobenzyl)isoquinolinium Bromide (119). The above procedure with 111 and p-nitrobenzyl bromide gave 2.1 g (44%) of 119 as a yellow solid, mp 225-227°d (methanol); ir (#13090, KBr) Appendix, A-45; nmr (#16210, d_6-DMSO) Appendix, B-38.

Anal. Calcd for $C_{24}H_{19}BrN_2O_4$: C, 60.13; H, 4.00; N, 5.85. Found: C, 60.17; H, 3.91; N, 5.96.

Preparation of 1-(3',4'-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (120). 1-(3',4'-Dimethoxybenzyl)-

2-methylisoquinolinium iodide (112) (1 g, 2.4 mmol) was added portionwise to a slurry of 1 g (28 mmol) of sodium borohydride in 50 ml of ethanol. The slurry was stirred at room temperature overnight. The excess sodium borohydride was decomposed with 10% hydrochloric acid and then 200 ml of water was added. The solution was made basic with 6N sodium hydroxide and extracted three times with 50 ml of chloroform. The combined extracts were dried over anhydrous potassium carbonate, filtered, and concentrated to yield 0.5 g (72%) of 120 as a brown oil; ir (#13164, film) Appendix, A-46; nmr (#12399, $DCCl_3$) Appendix, B-39. The product was analyzed as the picrate, mp 139-141° (ethanol).

Anal. Calcd for $C_{25}H_{26}N_4O_9$: C, 57.02; H, 4.97; N, 10.64. Found: C, 57.34; H, 5.02; N, 10.64.

General Procedure for the Preparation of 1,2-Disubstituted-1,2-dihydroisoquinolines. Following the procedure of Barton,[53] 3.0 mmol of the substituted isoquinolinium salt was added, portionwise, to a suspension of 0.5 g (0.013 mol) of sodium borohydride in 20 ml of dry pyridine. The mixture was stirred after each addition until complete solution was effected. A second portion of 0.4 g (0.011 mol) of sodium borohydride was then added to the solution and stirring was continued for 5 min. Ether (100 ml) and 75 ml of water were added, the layers were separated, and the aqueous layer was extracted twice with 50 ml of ether. The combined ether layers were dried over anhydrous potassium carbonate, filtered and evaporated to yield a yellow oil. The pyridine which

remained was removed under reduced pressure to give the substituted 1,2-dihydroisoquinoline (121-127) in quantitative yield. The nmr spectra of these compounds were similar to the spectra of 1,2-dihydroisoquinolines published by Neumeyer.[55] The oils were used without further purification.

Attempted Preparation of 2,3-Dimethoxy-N-methylpavinane (128). A. The procedure of Battersby and Binks[24] for their preparation of N-methylpavine was followed in the attempted synthesis of 128. A solution of 2.1 g (7.1 mmol) of 1-(3',4'-dimethoxybenzyl)-2-methyl-1,2-dihydroisoquinoline (121), 10.5 ml of 97% formic acid and 4.2 ml of 85% phosphoric acid was heated at reflux (120°) under a nitrogen atmosphere for 22 hr. The cooled mixture was diluted with 50 ml of water, and the white solid which precipitated was removed by filtration. The solid proved to be inorganic material (mp > 360°). The aqueous filtrate was extracted twice with 30 ml of chloroform to remove any non-basic material. After being made strongly alkaline with 20% ammonium hydroxide, the aqueous solution was extracted six times with 50 ml of chloroform. The combined extracts were dried over anhydrous potassium carbonate, filtered and concentrated to yield 1.6 g (76%) of brown oil. The ir spectrum (#19044), nmr spectrum (#12488, $DCCl_3$), and picrate derivative (mp 139-140.5°) were identical to those of 1-(3',4'-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (120).

B. 1-(3',4'-Dimethoxybenzyl)-2-methyl-1,2-dihydroisoquinoline (121) (0.3 g, 1 mmol) was treated with an excess

of each of the following reagents and stirred overnight at room temperature: a) acid washed Dowex-50 resin in ethanol; b) 1N trifluoroacetic acid in chloroform; c) 1N trichloroacetic acid in chloroform; d) 1N p-toluenesulfonic acid (anhydrous) in chloroform; and e) acid washed alumina in chloroform. The reactions were worked up as in the above procedure. In each case, nmr spectroscopy showed that the products contained no N-methyl signal. The products were not characterized further.

General Procedure for the Preparation of Pavinane Derivatives. The substituted 1-benzyl-1,2-dihydroisoquinoline (3.5 mmol) dissolved in 50 ml of chloroform was added dropwise over a period of 3 hr to a stirred mixture of 75 ml of chloroform and 40 ml of 70% aqueous perchloric acid under a nitrogen atmosphere. Stirring was continued at ambient temperature for 72 hr. The layers were separated, and 750 ml of water was added to the aqueous layer. After standing overnight, the perchlorate salt of the pavinane was collected by filtration, washed with water and dried. The base was prepared by dissolving the perchlorate salt in warm ethanol and adding 10% aqueous sodium hydroxide solution. Cooling caused the precipitation of the base which was collected by filtration.

2,3-Dimethoxy-N-methylpavinane (128). The above procedure with 121 gave 0.85 g (60%) of 128 as the perchlorate, mp 272-274°d (ethanol-acetonitrile); uv max (#1040, CH_3OH) 290 nm (shoulder), 280 nm (ε4500), 271 nm (shoulder).

Anal. Calcd for $C_{19}H_{22}ClNO_6$: C, 57.65; H, 5.60; N, 3.54. Found: C, 57.75; H, 5.63; N, 3.91.
The base was isolated as a white solid, mp 107-109° (methanol); ir (#13092, KBr) Appendix, A-47; nmr (#653, $DCCl_3$) Appendix, B-40. 128 was further characterized as the picrate, mp 241-243°d (ethanol-dimethylformamide).

Anal. Calcd for $C_{25}H_{24}N_4O_9$: C, 57.25; H, 4.61; N, 10.68. Found: C, 57.40; H, 4.64; N, 10.94.

2,3-Dimethoxy-N-benzylpavinane (129). The above procedure with 123 gave 0.75 g (50%) of 129 as the perchlorate, mp 120°d; uv max (#1043, CH_3OH) 280 (ε4800).

Anal. Calcd for $C_{25}H_{26}ClNO_6 \cdot 0.50\ H_2O$: C, 62.43; H, 5.66; N, 2.91. Found: C, 62.22; H, 5.44; N, 3.27.
The base was isolated as a brown solid; ir (#13283, KBr) Appendix, A-48; nmr (#767, $DCCl_3$) Appendix, B-41.

2,3-Dimethoxy-N-(4'-nitrobenzyl)pavinane (130). The above procedure with 124 gave 1.45 g (95%) of 130 as the perchlorate, mp 158-160°d (isopropanol); uv max (#1042, CH_3OH) 270 nm (ε12,200).

Anal. Calcd for $C_{25}H_{25}ClN_2O_8$: C, 58.02; H, 4.87; N, 5.42. Found: C, 58.17; H, 5.13; N, 5.64.
The base was isolated as a brown solid; ir (#13093, KBr) Appendix, A-49; nmr (#514, $DCCl_3$) Appendix, B-42.

2,3-Dimethoxy-N-(2',6'-dichlorobenzyl)pavinane (131). The above procedure with 125 gave 1.1 g (58%) of 131 as the perchlorate, mp 169°d (isopropanol); uv max (#1045, CH_3OH) 282 nm (ε5400). The base was isolated as a white solid,

mp 189-190° (methanol); uv max (#1044, CH_3OH) 281 nm (ϵ4700); ir (#13456, KBr) Appendix, A-50; nmr (#1045, $DCCl_3$) Appendix, B-43.

Anal. Calcd for $C_{25}H_{23}NO_2Cl_2$: C, 68.18; H, 5.26; N, 3.18. Found: C, 67.79; H, 5.46; N, 3.16.

Attempted Preparation of 2,3-Methylenedioxypavinanes. N-benzyl (126) and N-p-nitrobenzyl-1-(3,4-methylenedioxybenzyl)-1,2-dihydroisoquinoline (127) were subjected to the conditions of cyclization as described above. After stirring for only a few hours, the aqueous perchloric acid layers turned a purple and green color, respectively, indicating that cleavage of the methylenedioxy group had occurred. Only unidentifiable tars were isolated from these reactions.

Preparation of 1-Skatylisoquinoline (149). The compound was prepared by the procedure of Boekelheide.[91] To a solution of 8.6 g (0.05 mol) of gramine and 13.0 g (0.05 mol) of 1-cyano-2-benzoyl-1,2-dihydroisoquinoline (108) in 100 ml of xylene was added a small piece of sodium. The mixture was heated under reflux in a nitrogen atmosphere for 3 hr and then filtered while hot. After evaporation of the xylene, 200 ml of ethanol and 40 ml of 10% sodium hydroxide were added, and the solution was heated under reflux for 2 hr. Most of the solvent was evaporated, and the residue was stirred in 300 ml of water. The resulting, brick-red solid was collected by filtration, washed with water, and dried to give 16 g of very crude product. This solid was eluted with benzene from a 50 mm diameter column packed with 320 g of neutral alumina. One

recrystallization from ethanol gave 7.1 g (55%) of pure 149 as a white solid, mp 171-174°, lit.[91] mp 171-172°; ir (#12143, KBr) 3200 (b), 1620 (m), 1590 (w), 1550 (m), 1440 (s), 1340 (s), 1260 (m), 1230 (m), 1005 (s), 915 (s), 880 (m), 835 (s), 810 (s), 750 (b); nmr (#10559, $DCCl_3$) δ 8.68-6.66 (m, 12H), 4.84 (s, 2H).

Preparation of 1-Skatyl-2-methylisoquinolinium Iodide (150). A solution of 5.2 g (0.02 mol) of 1-skatylisoquinoline (149) in 40 ml of methyl iodide was converted quantitatively to the quaternary salt by heating under reflux under a nitrogen atmosphere for 4 hr. The excess iodomethane was removed by distillation and the yellow solid was collected by filtration, washed with ether, and dried to give 150, mp 234-237°d, lit.[91] mp 227-228°d; ir (#12144, KBr) 3300 (s), 1645 (s), 1570 (w), 1505 (w), 1350 (m), 1230 (m), 1100 (w), 885 (w), 825 (m), 760 (b). No further purification was necessary.

Preparation of 14-Methyl-6,7,12,13-tetrahydro-6,12-imino-5H-benzo[5,6]cyclooct[1,2-b]indole (152). A solution of 1.1 g (4.0 mmol) of 1-skatyl-2-methyl-1,2-dihydroisoquinoline (151) in 50 ml of diethyl ether and 1 ml of methanol was added dropwise over a 15 min period to a stirred slurry of 75 ml of diethyl ether and 40 ml of 1N hydrochloric acid under a nitrogen atmosphere at ambient temperature. After the addition was complete, the slurry was stirred for 1 hr. The layers were separated, and the aqueous layer was made basic with concentrated ammonium hydroxide. The solid which precipitated

was removed by filtration, washed with water and dried to yield 1.1 g (quantitative) of 152; ir (#13325, KBr) Appendix, A-51; nmr (#797, $DCCl_3$) Appendix, B-44. This compound decomposed readily and was quickly converted to the methiodide (153), mp 255-258°d.

Anal. Calcd for $C_{20}H_{21}IN_2 \cdot H_2O$: C, 55.30; H, 5.34; N, 6.45. Found: C, 55.18; H, 5.09; N, 6.50.

Preparation of 2-Indanone (142). This compound was prepared according to the procedure in Organic Syntheses[59] and 85.3 g (65%) of 142 as a white solid, mp 53-55°, lit.[59] mp 57-58°, was obtained; ir (#12656, KBr) 3050 (w), 2900 (w), 1750 (s), 1465 (m), 1390 (m), 1300 (m), 1185 (m), 1150 (m), 1065 (w), 980 (m), 800 (w), 745 (b); nmr (#14908, CCl_4) δ 7.19 (s, 4H), 3.37 (s, 4H).

Preparation of 2-Indanonoxime (143). This compound was prepared according to the procedure of Rosen and Green.[92] A solution of 6.4 g (0.092 mol) of hydroxylamine hydrochloride in a mixture of 10 ml of ethanol and 10 ml of water was added to a stirred solution of 10.0 g (0.076 mol) of 2-indanone (142) in 25 ml of pyridine. The reaction mixture immediately turned warm and a white solid precipitated. After 0.5 hr, the suspension was diluted with 200 ml of water and the white solid was collected by filtration and dried to yield 10.9 g (97%) of 143 as white needles, mp 152-153°, lit.[92] 153-154.5°; ir (#12640, KBr) 3300 (b), 2850 (s), 1650 (w), 1440 (m), 1400 (m), 1300 (w), 1210 (w), 1165 (w), 1020 (w), 950 (b), 855 (w), 730 (b); nmr (#14943, d_6-DMSO)

δ 7.20 (s, 4H), 3.74 (s, 4H).

Preparation of 1,4-Dihydro-3-[2H]isoquinolone (144). The Beckman rearrangement was carried out according to the general procedure outlined by Donaruma and Heldt.[61] To a cooled, stirred solution of 3.0 g (0.02 mol) of 2-indanonoxime (143) in 150 ml of dry ether was added 6.2 g (0.03 mol) of phosphorus pentachloride. The slurry was stirred overnight at room temperature and then poured onto crushed ice. The ether was evaporated and the aqueous solution was extracted with chloroform. The extracts were dried over anhydrous magnesium sulfate, filtered and the filtrate was concentrated to give a black solid as residue. It was sublimed at 145°/25 mm to yield 2.1 g (70%) of 144 as yellow needles, mp 149-150°, lit.[93] mp 150-152°; ir (#12641, KBr) 3250 (s), 3050 (s), 2950 (s), 1650 (s), 1490 (s), 1450 (w), 1425 (m), 1395 (m), 1340 (s), 1320 (m), 1250 (m), 1190 (m), 1100 (m), 1040 (w), 980 (w), 955 (w), 895 (w), 835 (b), 750 (b); nmr (#14942, $DCCl_3$) δ 8.18 (s, 1H), 7.22 (s, 4H), 4.50 (s, 2H), 3.57 (m, 2H).

Preparation of 1-Benzyl-2-indanonoxime (146). 1-Benzyl-2-indanone was prepared by a modification of the procedure of Blomquist and Moriconi.[60a] In a three-necked, 500 ml flask fitted with a magnetic stirrer, Dean-Stark trap, reflux condenser, nitrogen inlet tube and heating mantel, a solution of 20 g (0.20 mol) of hexamethyleneimine and 100 ml of benzene was heated under reflux until all the water was removed (2 hr). 2-Indanone (142) (13.2 g, 0.10 mol) was added in one portion

and the solution was heated under reflux overnight. The yellow solution was concentrated and the enamine was dissolved in 100 ml of a solution of 1:1::dioxane:tetrahydrofuran. Benzyl bromide (25.6 g, 0.15 mol) was added dropwise over a 0.5 hr period, and the solution was heated under reflux for 5 hr. After cooling, the white iminium salt was filtered, washed with tetrahydrofuran, and immediately stirred in a solution of 10 ml of acetic acid in 200 ml of water and heated under reflux under a nitrogen atmosphere for 1 hr. After cooling, the aqueous mixture was extracted three times with 50 ml of ether. The combined extracts were dried over anhydrous sodium sulfate, filtered and the filtrate concentrated to yield 10.9 g of crude 1-benzyl-2-indanone (145).

Since most 2-indanones are easily oxidized by air, the ketone was dissolved in 25 ml of pyridine and to this solution was added 6.4 g (0.092 mol) of hydroxylamine hydrochloride dissolved in 10 ml of water and 10 ml of ethanol. After stirring overnight at room temperature, under a nitrogen atmosphere, 300 ml of water was added and the aqueous mixture was extracted three times with 75 ml of chloroform. The combined extracts were dried over anhydrous potassium carbonate, filtered and the filtrate was concentrated to yield a brown oil. This oil solidified to a gummy solid when stirred with low boiling petroleum ether at ice bath temperatures. The solid was chromatographed and eluted with benzene-ether (1:1) from a neutral alumina column to yield 5.9 g (25% from 2-indanone) of 146. An analytical sample, mp 129-131°, was recrystallized from hexane; ir (#12642, KBr)

Appendix, A-52; nmr (#15059, $DCCl_3$) Appendix, B-45.

Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 81.38; H, 6.34; N, 5.85.

BIBLIOGRAPHY

1. (a) H. Kessler, Angew. Chem. Int. Ed. Engl., 9, 219 (1970); (b) A. Rauk, L. C. Allen, and K. Mislow, ibid., 9, 400 (1970).

2. (a) D. M. Dennison and G. E. Uhlenbeck, Phys. Rev., 41, 313 (1932); (b) R. S. Berry, J. Chem. Phys., 32, 933 (1960).

3. (a) J. M. Lehn and J. Wagner, Chem. Commun., 148 (1968); (b) J. B. Lambert and W. L. Oliver, J. Amer. Chem. Soc., 91, 7774 (1969); (c) A. Loewenstein, J. F. Neumer, and J. D. Roberts, ibid., 82, 3599 (1960); (d) A. T. Bottini and J. D. Roberts, ibid., 80, 5203 (1958); (e) S. J. Brois, ibid., 89, 4242 (1967).

4. F. A. L. Anet and J. M. Osyany, ibid., 89, 352 (1967).

5. S. J. Brois, Trans. N. Y. Acad. Sci., 31, 931 (1969).

6. H. A. Bent, Chem. Rev., 61, 275 (1961).

7. V. Rautenstrauch, Chem. Commun., 713 (1969).

8. J. D. Andose, J. M. Lehn, K. Mislow, and J. Wagner, J. Amer. Chem. Soc., 92, 4050 (1970).

9. (a) C. L. Closs, ibid., 81, 5456 (1959); (b) D. L. Griffith and J. D. Roberts, ibid., 87, 4089 (1965); (c) J. C. N. Ma and E. W. Warnoff, Can. J. Chem., 43, 1849 (1965).

10. M. Saunders and F. Yamada, J. Amer. Chem. Soc., 85, 1882 (1963).

11. (a) H. E. Simmons and C. H. Park, ibid., 90, 2428 (1968); (b) ibid., 90, 2429 (1968); (c) ibid., 90, 2431 (1968).

12. R. E. Lyle and C. R. Ellefson, ibid., 89, 4563 (1967).

13. G. W. Gribble, N. R. Easton, Jr., and J. T. Easton, Tetrahedron Lett., 1075 (1970).

14. (a) S. P. McGlynn, Chem. Rev., 58, 1113 (1958); (b) G. Briegleb, "Electronen-Donator-Acceptor-Komplexe", Springer-Verlag, Berlin, 1961; (c) E. M. Kosower in "Progress in Physical Organic Chemistry", Vol. 3, S. G. Cohen, A. Streitwieser, and R. W. Taft, Eds., Interscience, New York, 1965, p 81; (d) R. S. Mulliken and W. B. Person in "Annual Reviews of Physical Chemistry", Vol. 13, H. Erying, Ed., Annual Reviews, Inc., Palo Alto, 1962, p 107; (e) L. J. Andrews and R. M. Keefer, "Molecular Complexes in Organic Chemistry", Holden-Day,

San Francisco, 1964; (f) J. Rose, "Molecular Complexes", Pergamon Press, New York, 1967; (g) R. S. Mulliken and W. B. Person, "Molecular Complexes", Wiley, New York, 1969; (h) R. Foster, "Organic Charge-transfer Complexes", Academic Press, New York, 1969.

15. (a) W. N. White, J. Amer. Chem. Soc., 81, 2912 (1959); (b) R. Carruthers, F. M. Dean, L. E. Houghton, and A. Ledwith, Chem. Commun., 1206 (1967); (c) M. Oki and K. Mutai, Tetrahedron Lett., 2019 (1968); (d) H. A. H. Craenen, J. W. Verhoeven, and Th. J. de Boer, ibid., 1167 (1970); (e) M. Oki and K. Mutai, Tetrahedron, 26, 1181 (1970); (f) K. Mutai, Tetrahedron Lett., 1125 (1971); (g) R. Est-Stammer and J. B. F. N. Engberts, ibid., 3215 (1971); (h) J. H. Borkent, J. W. Verhoeven, and Th. J. de Boer, ibid., 3363 (1972); (i) K. Mutai, Bull. Chem. Soc. Jap., 45, 2635 (1972); (j) L. G. Schriff, A. J. A. Weerdt, D. J. H. Staalman, J. W. Verhoeven, and Th. J. de Boer, Tetrahedron Lett., 1649 (1973); (k) R. Est-Stammer and J. B. F. N. Enberts, Can. J. Chem., 51, 1187 (1973).

16. (a) E. Prudhommeaux, C. Viel, and B. Delbarre, Chim. Ther., 6, 358 (1971); (b) P. Bouvier, M. Marcot, C. Viel, B. Delbarre, and G. Duman, ibid., 6, 462 (1971); (c) C. Izard-Verchere and C. Viel, ibid., 6, 469 (1971).

17. W. J. Burke, J. Amer. Chem. Soc., 71, 609 (1949).

18. M. E. Kuehne and E. A. Konopka, J. Med. and Pharm. Chem., 5, 257 (1962).

19. (a) Y. Allingham, R. C. Cookson, T. A. Crabb, and S. Vary, Tetrahedron, 24, 4625 (1968); (b) J. E. Anderson and J. B. Roberts, J. Amer. Chem. Soc., 90, 4186 (1968); (c) R. O. Hutchins, L. D. Kopp, and E. L. Eliel, ibid., 90, 7174 (1968); (d) R. A. Y. Jones, A. R. Katritzky, and M. Snarey, J. Chem. Soc., B, 131 (1970); (f) ibid., 135 (1970); (g) E. L. Eliel, Acc. Chem. Res., 3, 1 (1970).

20. D. Ginsburg, "The Opium Alkaloids", Interscience, New York, 1962.

21. F. Santavy in "The Alkaloids", Vol. 12, R. H. F. Manske, Ed., Academic Press, New York, 1970, Chapter 5.

22. (a) H. Goldschmiedt, Monatsh. Chem., 7, 485 (1886); (b) ibid., 19, 324 (1898).

23. (a) C. Schopf, Experientia, 5, 201 (1949); (b) C. Schopf, Angew. Chem., 62, 453 (1950).

24. A. R. Battersby and R. Binks, J. Chem. Soc., 2888 (1955).

25. F. R. Stermitz, S-Y. Lwo, and G. Kallos, J. Amer. Chem. Soc., 85, 1551 (1963).

26. M. J. Martell, T. O. Soine, and L. B. Kier, ibid., 85, 1022 (1963).

27. H. Zinnes, F. R. Zuleski, and J. Shavel, Jr.*, J. Org. Chem., 33, 3605 (1968).

28. M. Sainsbury, D. W. Brown, S. F. Dyke,* R. G. Kinsman, and B. J. Moon, Tetrahedron, 24, 6695 (1968).

29. J. Shavel and H. Zinnes, U. S. Patent 3518270 (1970); Chem. Abstr., 73, 56084e (1970).

30. K. A. Jaeggi, K. Kocsis, and U. Renner, German Patent 2026486 (1970); Chem. Abstr., 74, 53568a (1970).

31. C-H. Chen and T. O. Soine, J. Pharm. Sci., 61, 55 (1972).

32. S. F. Dyke in "Advances in Heterocyclic Chemistry", Vol. 9, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, 1968, p 1.

33. J. Knabe, R. Dorr, S. F. Dyke, and R. G. Kinsman, Tetrahedron Lett., 5373 (1972).

34. M. P. Cava, C. K. Wilkins, Jr., D. R. Dalton, and K. Bissho, J. Org. Chem., 30, 3772 (1965).

35. H. L. Holmes in "Organic Reactions", Vol. 4, R. Adams, Ed., John Wiley and Sons, Inc., New York, 1948, Chapter 2.

36. J. S. Meek, P. A. Monroe, and C. J. Bouboulis, J. Org. Chem., 28, 2572 (1963).

37. C. Wilkins, Tetrahedron Lett., 4817 (1965).

38. R. E. Lyle and P. S. Andersen in "Advances in Heterocyclic Chemistry", Vol. 6, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, 1966, p 46.

39. (a) G. Zweifel and H. C. Brown in "Organic Reactions", Vol. 13, A. C. Cope, Ed., John Wiley and Sons, Inc., New York, 1963, pp 1-54; (b) H. C. Brown and P. Heim, J. Amer. Chem. Soc., 86, 3566 (1964).

40. M. R. Crampton in "Advances in Physical Organic Chemistry", Vol. 7, V. Gold, Ed., Academic Press, New York, 1969, p 211.

41. K. Mislow, "Introduction to Stereochemistry", W. A. Benjamin, Inc., New York, 1966.

42. M. Pailer and W. Fenzyl, Monatsh. Chem., 92, 1295 (1961).

43. B. M. Mikhailov and L. S. Povarov, Zh. Obshch. Kim., 41, 1540 (1971), Chem. Abstr., 75, 129425v (1971).

44. R. Adams, M. F. Fogler, and C. W. Kreger, J. Amer. Chem. Soc., 44, 1127 (1922).

45. R. Merten and G. Müller, Chem. Ber., 97, 682 (1964).

46. R. K. Razdan, H. G. Pars, B. A. Zitko, V. V. Kane, and W. R. Thompson, Tetrahedron Lett., 1623 (1973).

47. H. Stetter and K. Heckel, ibid., 801 (1972).

48. A. C. Cope and S. W. Fenton, J. Amer. Chem. Soc., 73, 1673 (1951).

49. E. Cioranescu, A. Bucur, M. Elian, and C. D. Nenitzescu, Rev. Roum. Chim., 10, 149 (1965).

50. (a) W. E. McEwen and R. L. Cobb, Chem. Rev., 55, 511 (1955); (b) F. D. Popp in "Advances in Heterocyclic Chemistry", Vol. 9, A. R. Katritzky and A. J. Boulton, Eds., Academic Press, New York, 1968, p 1.

51. F. D. Popp and W. Blount, Chem. Ind. (London), 550 (1961).

52. (a) F. D. Popp and J. M. Wefer, Chem. Commun., 207 (1966); (b) J. Heterocyl. Chem., 4, 183 (1967); (c) J. R. Kershaw and B. C. Uff, Chem. Commun., 331 (1966); (d) J. Chem. Soc., 666 (1969).

53. D. H. R. Barton, R. H. Hesse, and G. W. Kirby, ibid., 6379 (1965).

54. R. Grewe, A. Mondon, and E. Nolte, Justus Liebigs Ann. Chem., 546, 161 (1949).

55. J. L. Neumeyer, M. McCarthy, K. K. Weinhardt, and P. L. Levins, J. Org. Chem., 33, 2890 (1968).

56. F. R. Stermitz and D. K. Williams, ibid., 38, 2099 (1973).

57. (a) R. H. F. Manske, K. H. Shin, A. R. Battersby, and D. F. Shaw, Can. J. Chem., 43, 2183 (1965); (b) A. C. Barker and A. R. Battersby, J. Chem. Soc., 1317 (1967).

58. (a) J. Knabe, J. Kubitz and N. Ruppenthal, Angew. Chem., 75, 981 (1963); (b) Angew. Chem. Int. Ed. Engl., 2, 689 (1963); (c) J. Knabe and J. Kubitz, Arch. Pharm. (Weinheim), 297, 129 (1964).

59. J. E. Horan and R. W. Schiessler in "Organic Syntheses", Vol. 41, J. D. Roberts, Ed., John Wiley and Sons, Inc., New York, p 53.

60. (a) A. T. Blomquist and E. J. Moriconi, J. Org. Chem., 26, 3761 (1961); (b) P. S. Anderson, G. F. Lundell, J. L. Cías, and F. M. Robinson, Tetrahedron Lett., 2787 (1971).

61. L. G. Donaruma and W. Z, Heldt in "Organic Reactions", Vol. 11, A. C. Cope, Ed., John Wiley and Sons, Inc., New York, 1960, Chapter 1.

62. M. J. Martell, Jr., T. O. Soine, and L. B. Kier, J. Pharm. Sci., 56, 973 (1967).

63. (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York, 1959, p 132; (b) L. M. Jackman, "Applications of Nuclear Magnetic Resonance in Organic Chemistry", Pergamon Press, New York, 1959, p 90.

64. F. A. L. Anet, Can. J. Chem., 39, 789 (1961).

65. M. Karplus, J. Chem. Phys., 30, 11 (1959).

66. C. H. Chen, T. O. Soine, and K. H. Lee, J. Pharm. Sci., 60, 1634 (1971).

67. H. O. House, R. W. Magin, H. W. Thompson, J. Org. Chem., 28, 2401 (1963).

68. (a) J. S. Waugh and R. W. Fessenden, J. Amer. Chem. Soc., 79, 846 (1957); (b) D. J. Cram, C. K. Dalton, and G. R. Knox, ibid., 85, 1088 (1963).

69. H. E. Carter, R. L. Frank, and H. W. Johnston in "Organic Syntheses", Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, 1955, p 168.

70. J. E. Baldwin and J. A. Duncan, J. Org. Chem., 36, 627 (1971).

71. (a) G. N. Walker, M. H. Moore, and B. N. Weaver, J. Org. Chem., 26, 2740 (1961); (b) P. Mamalis, J. Green, D. J. Outred, and M. J. Rix, J. Chem. Soc., 1829 (1965).

72. F. Kuffner, G. Lenneis, and H. Bauer, Monatsh. Chem., 91, 1152 (1960); Chem. Abstr., 55, 14494c (1961).

73. F. D. Popp and W. E. McEwen, J. Amer. Chem. Soc., 79, 3773 (1957).

74. S. Hoogewerff and W. A. von Dorp, Rec. Trav. Chim. des Pays-Bas, 5, 307 (1886).

75. F. Krohnke, Chem. Ber., 68, 1351 (1935).

76. F. Krohnke, ibid., 84, 388 (1951).

77. J. H. Chapman, P. G. Holton, A. C. Ritchie, T. Walker, G. B. Webb, and K. D. E. Whiting, J. Chem. Soc., 2471 (1962).

78. S. Kimoto and M. Okamoto, Chem. Pharm. Bull., 9, 480 (1961); Chem. Abstr., 55, 25946b (1961).

79. J. S. Buck, J. Amer. Chem. Soc., 56, 1769 (1934).

80. D. W. Brown and S. F. Dyke, Tetrahedron, 22, 2437 (1966).

81. H. Kondo and H. Ochiai, J. Pharm. Soc. Japan, 495, 313 (1923); Chem. Abstr., 17, 3032 (1923).

82. J. M. Bobbitt, J. M. Keely, K. L. Khanna, and R. Ebermann, J. Org. Chem., 30, 2247 (1965).

83. J. Knabe and G. Grund, Arch. Pharm., 296, 820 (1963); Chem. Abstr., 60, 7994a (1964).

84. N. J. Leonard and E. W. Nommensen, J. Amer. Chem. Soc., 71, 1808 (1949).

85. J. Graymore and D. R. Davis, J. Chem. Soc., 293 (1945).

86. J. Graymore, ibid., 1116 (1947).

87. J. S. Morley, ibid., 1414 (1961).

88. T. Naito and R. Dohmori, Japanese Patent 9380 (1956); Chem. Abstr., 52, 14688d (1958).

89. F. R. Gass, W. Hankart, and C. K. Ingold, J. Chem. Soc., 250 (1927).

90. Authentic samples of 1-(3',4'-dimethoxybenzyl)isoquinoline (110) and 1-(3',4'-methylenedioxybenzyl)isoquinoline (111) were generously supplied by Dr. John L. Neumeyer.

91. V. Boekelheide and C. Ainsworth, J. Amer. Chem. Soc., 72, 2134 (1950).

92. W. E. Rosen and M. J. Green, J. Org. Chem., 28, 2797 (1963).

93. (a) Y. C. Kim, Can. J. Chem., 47, 3259 (1969); (b) R. Huisgen and J. Reinertshofer, Justus Liebigs Ann. Chem., 575, 197 (1952).

94. T. Naokawa, K. Ishii, and H. Kakuichi, Kogyo Kagaku Zasshi, 66, 514 (1963); Chem. Abstr., 59, 15398d (1963).

95. J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", Prentice-Hall, Inc., Englewood Cliffs, 1965, p 82.

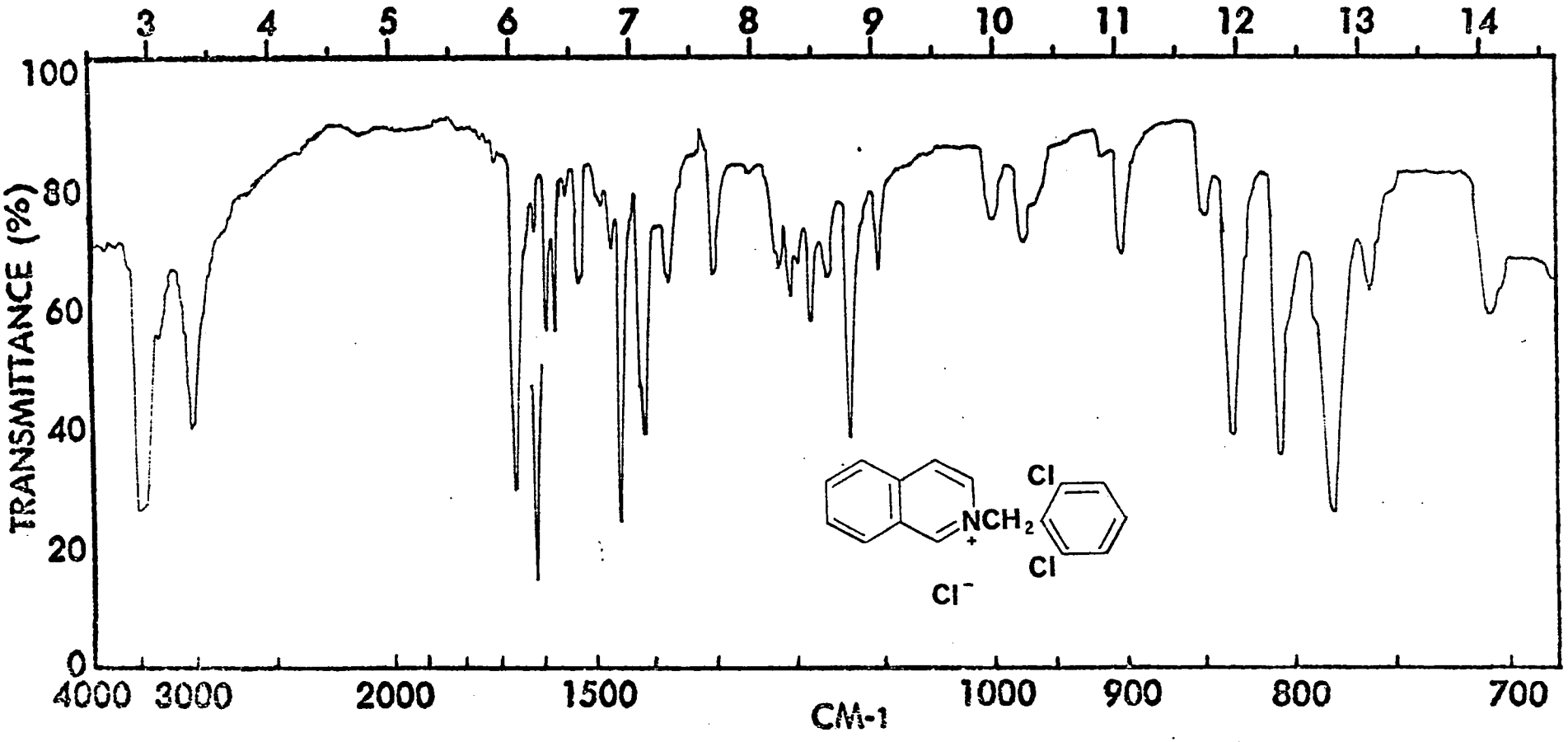
96. This nomenclature was suggested by Dr. Kurt Loening, Chemical Abstracts Service, Columbus, Ohio.

*Senior Author

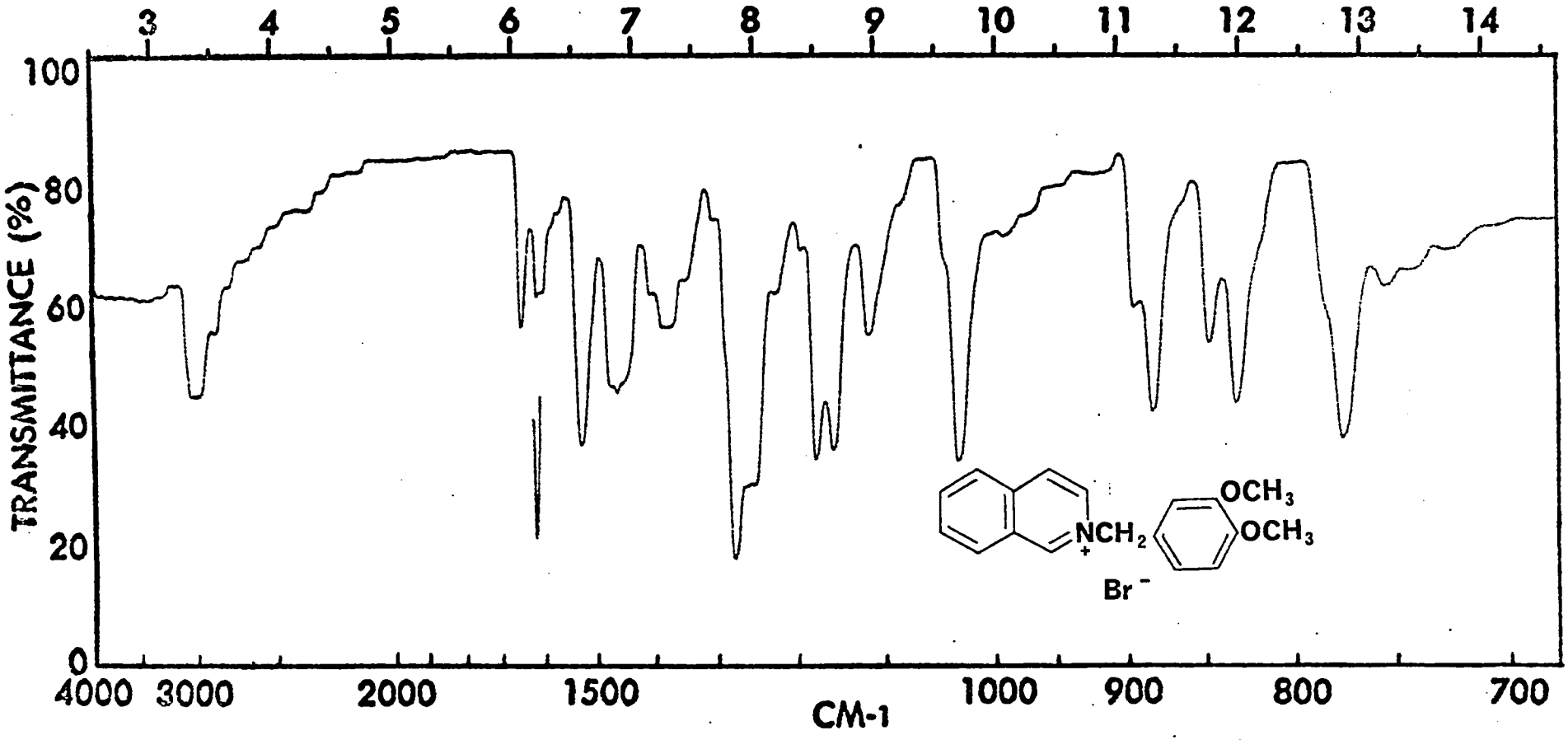
APPENDIX

A. Infrared Spectra

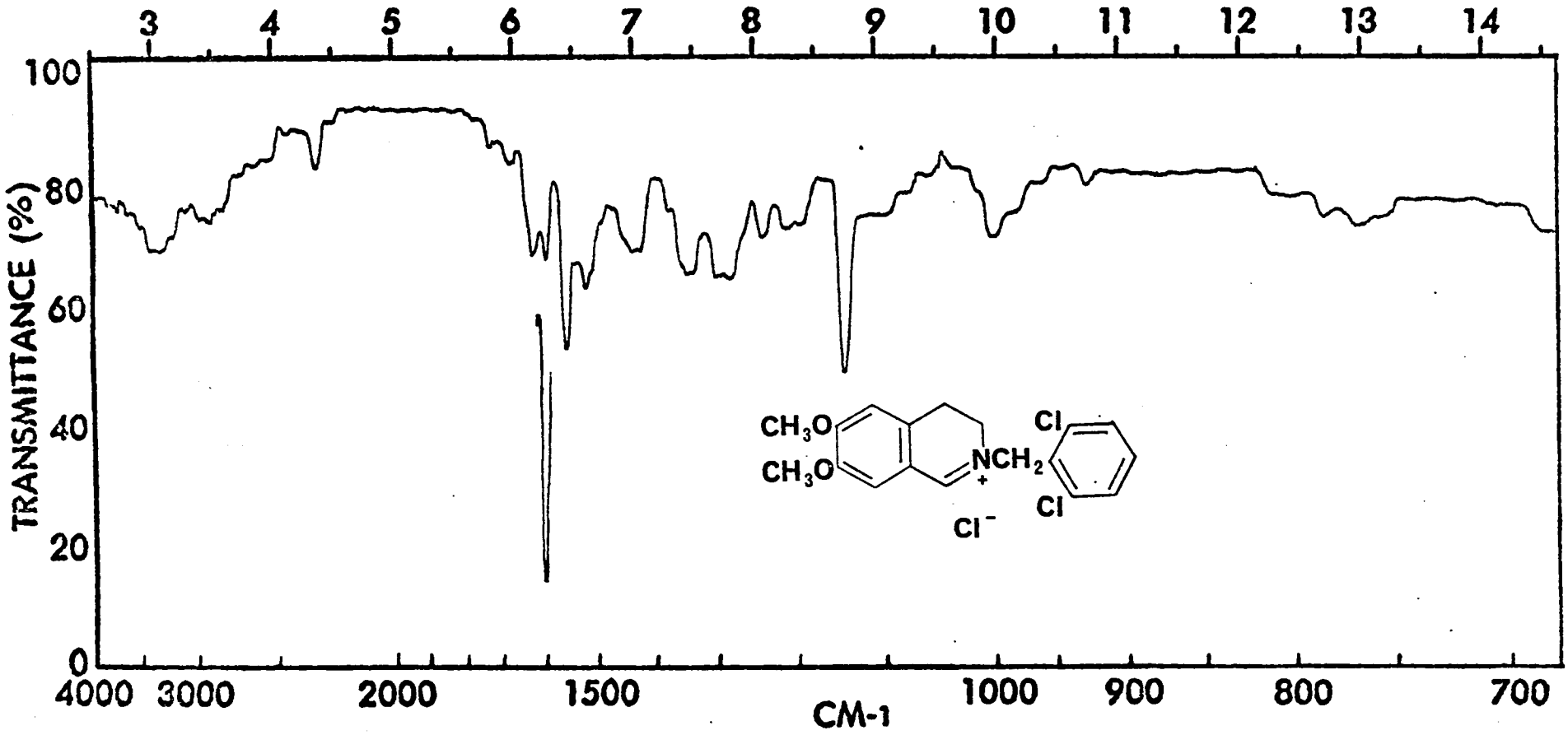
B. Nuclear Magnetic Resonance Spectra



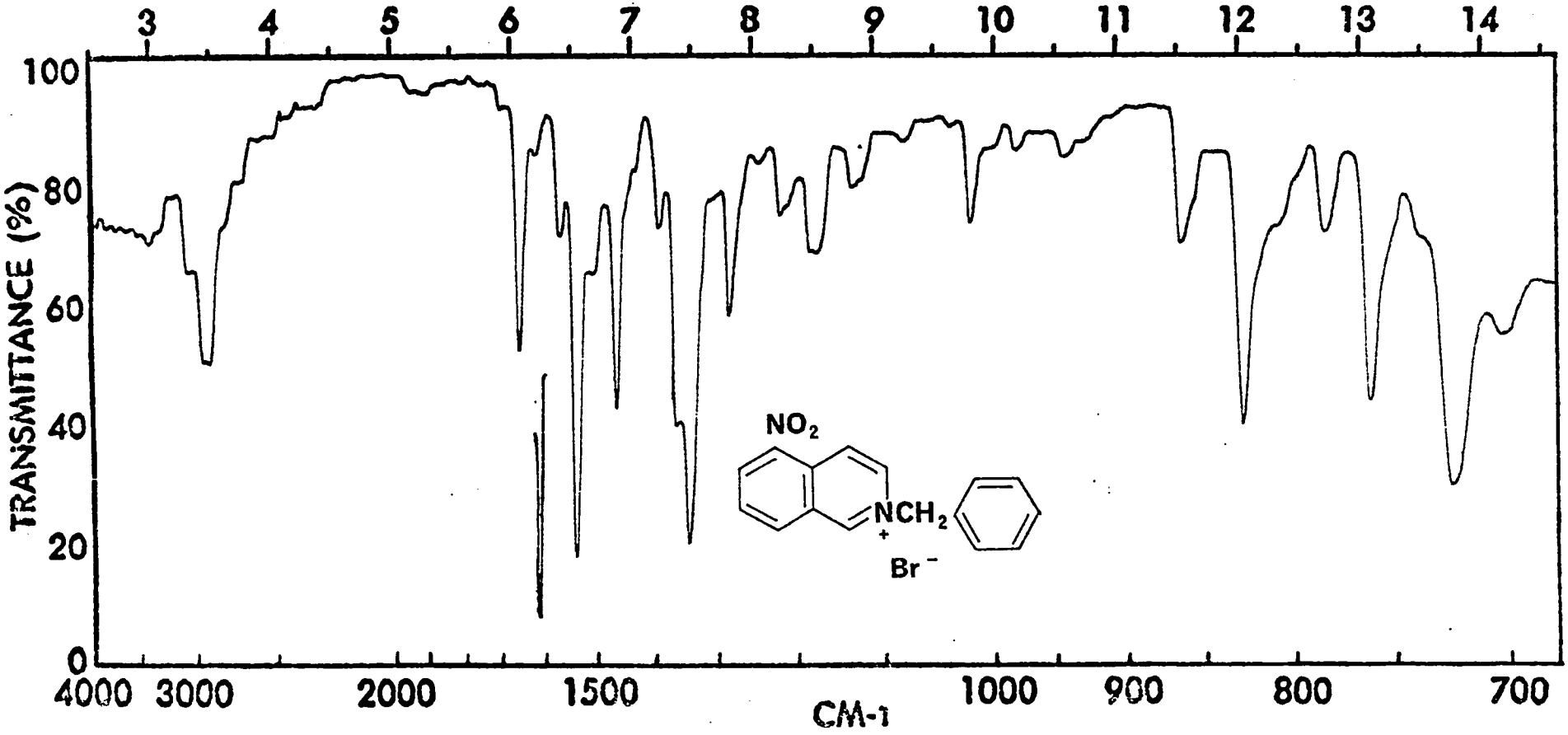
A-1. 2-(2',6'-Dichlorobenzyl)isoquinolinium Chloride (27).



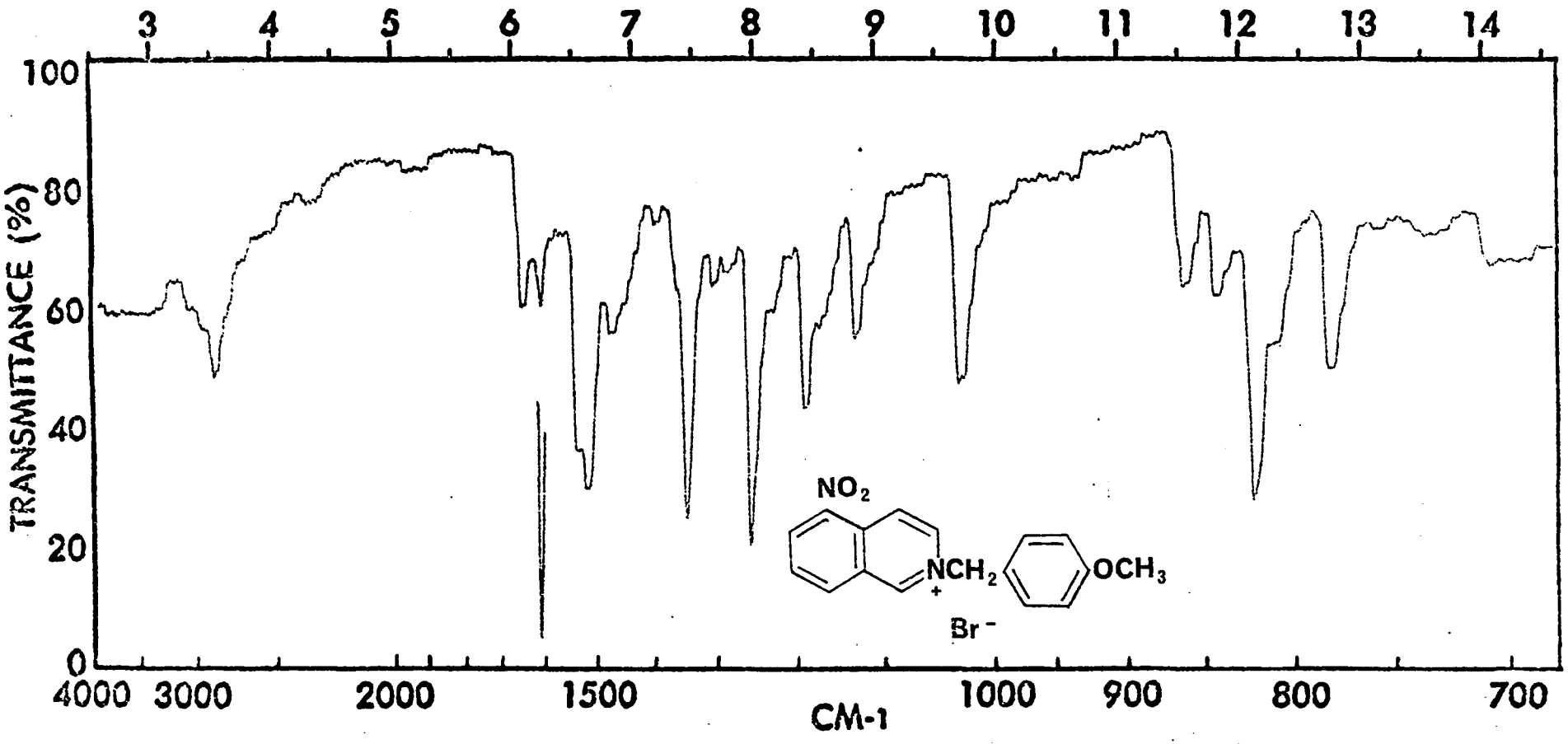
A-2. 2-(3',4'-Dimethoxybenzyl)isoquinolinium Bromide (30).



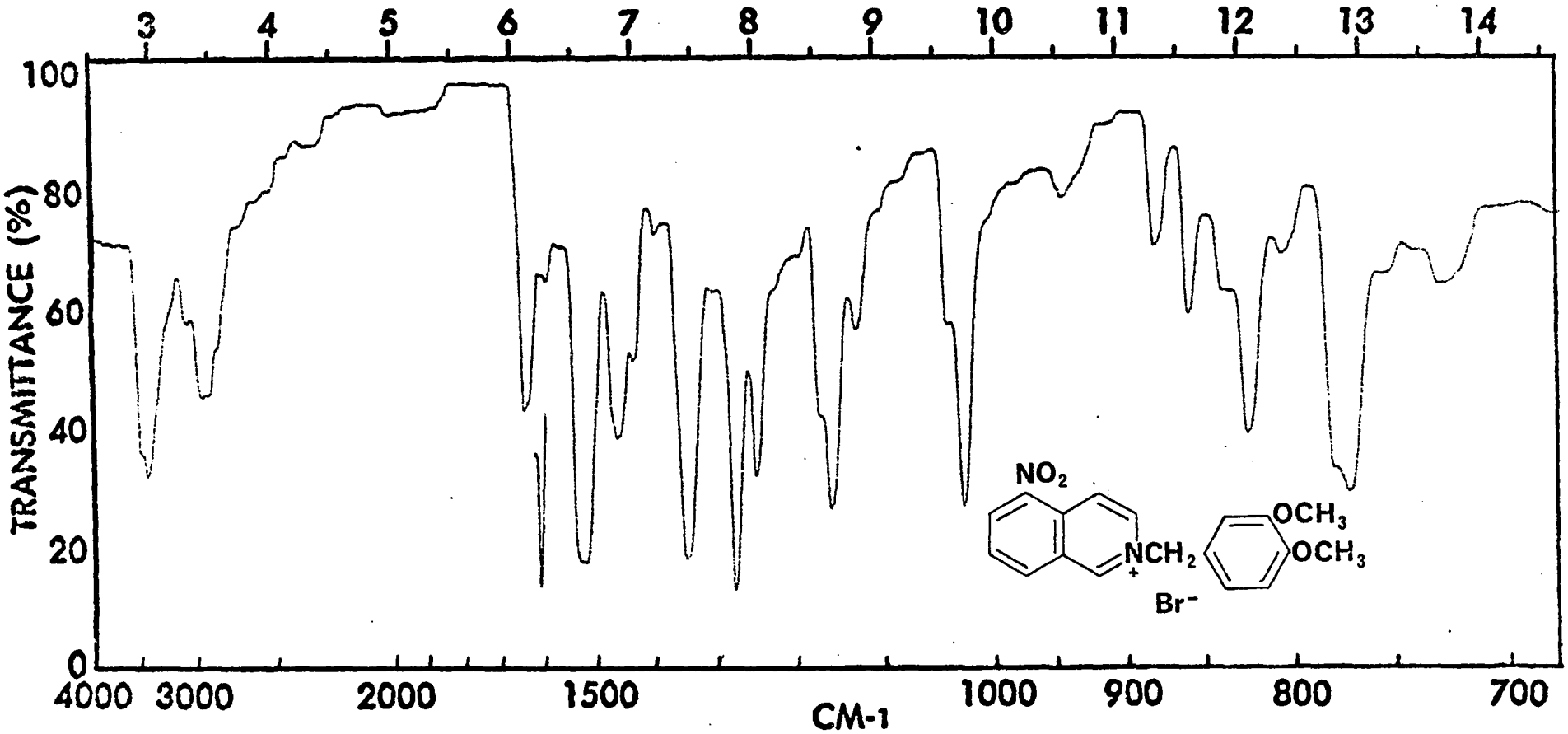
A-3. 2-(2',6'-Dichlorobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinolinium Chloride (32).



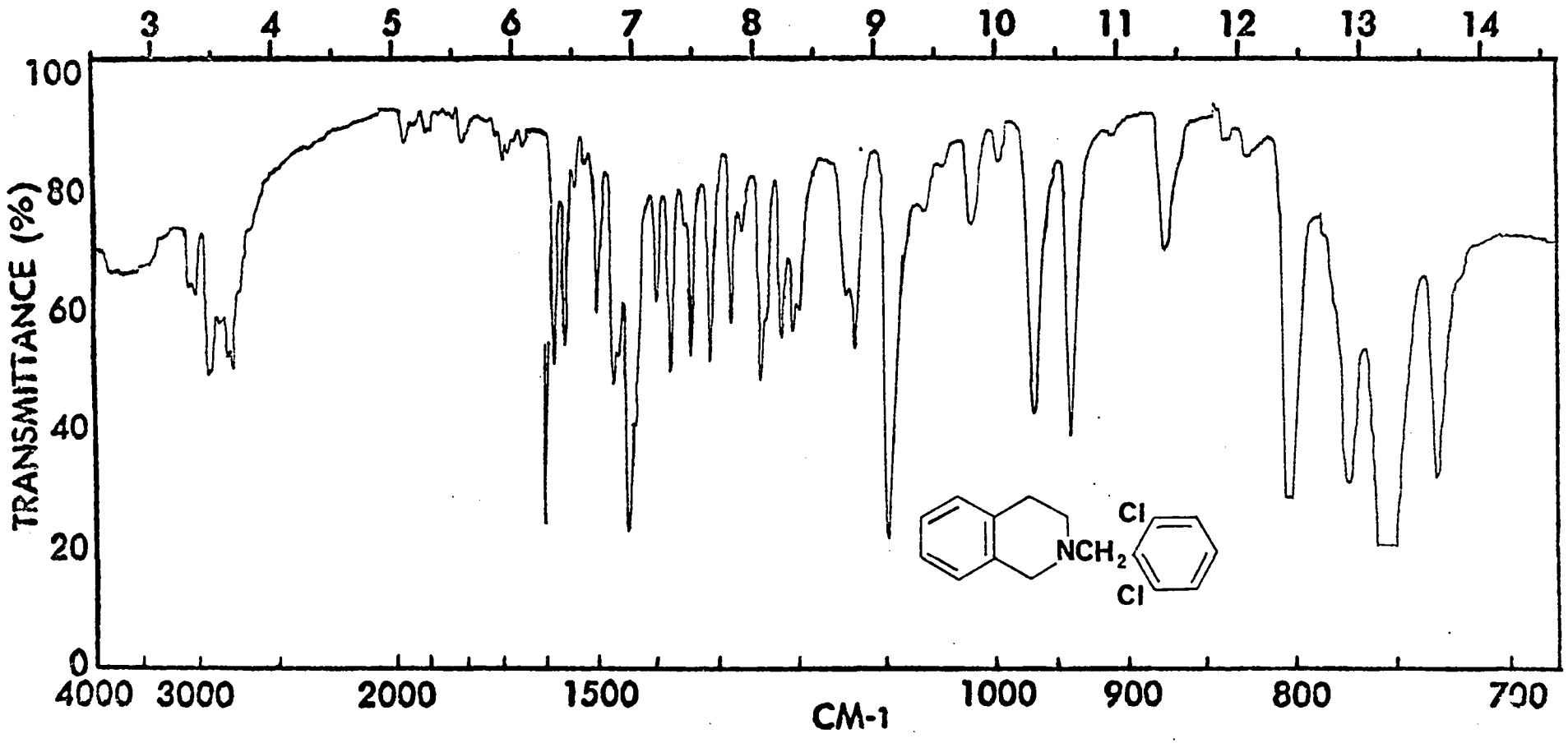
A-4. 2-Benzyl-5-nitroisoquinolinium Bromide (34).



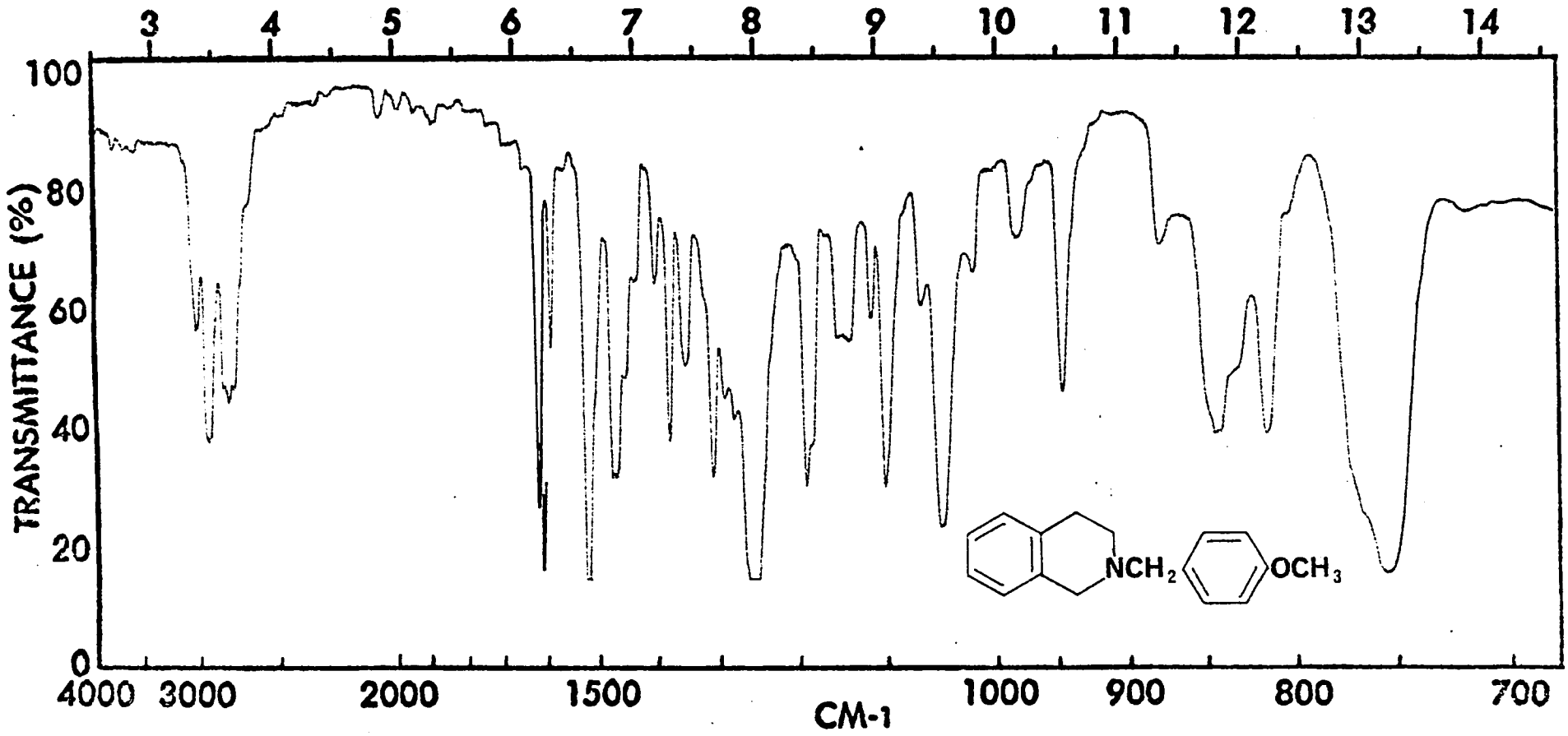
A-5. 2-(4'-Methoxybenzyl)-5-nitroisoquinolinium Bromide (35).



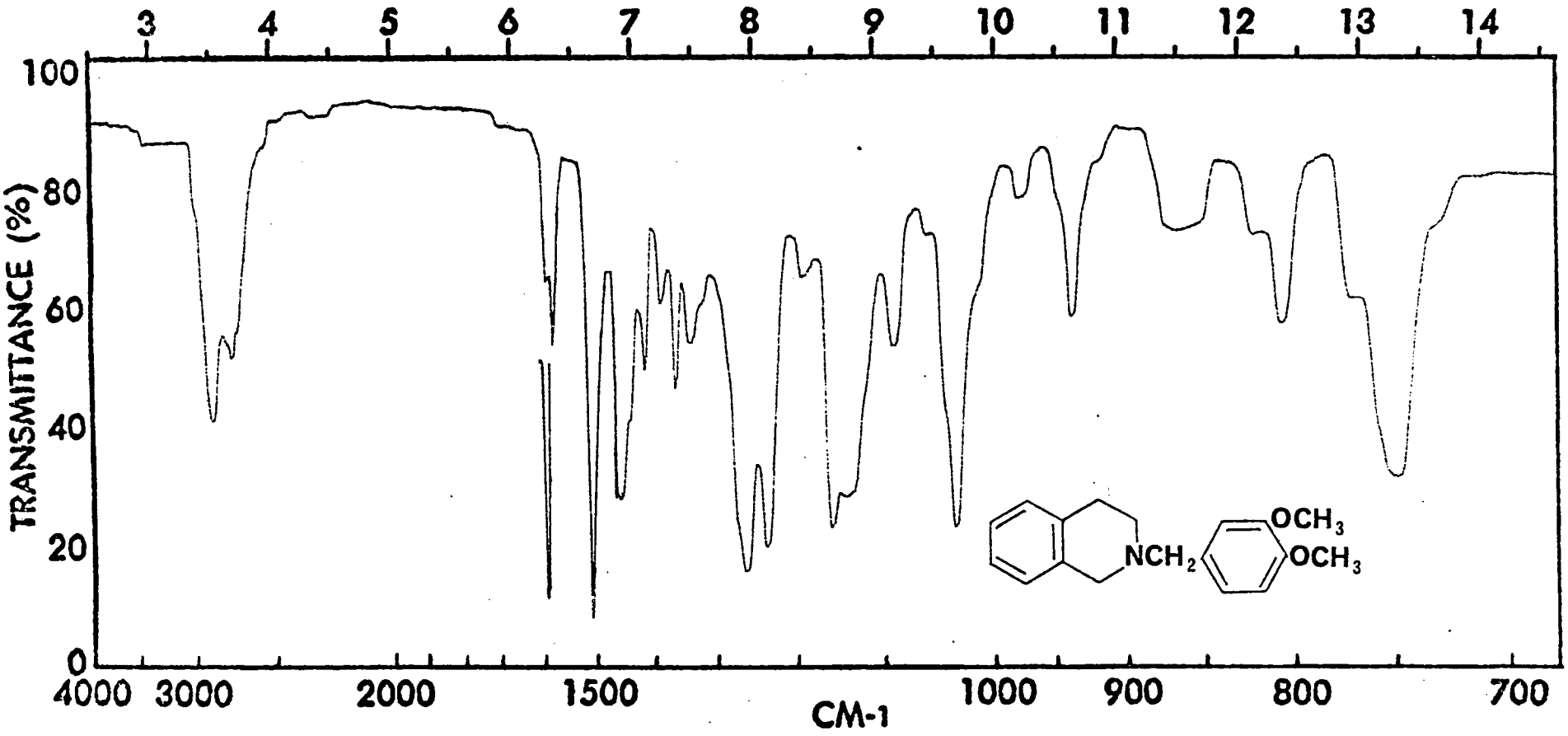
A-6. 2-(3',4'-Dimethoxybenzyl)-5-nitroisoquinolinium Bromide (36).



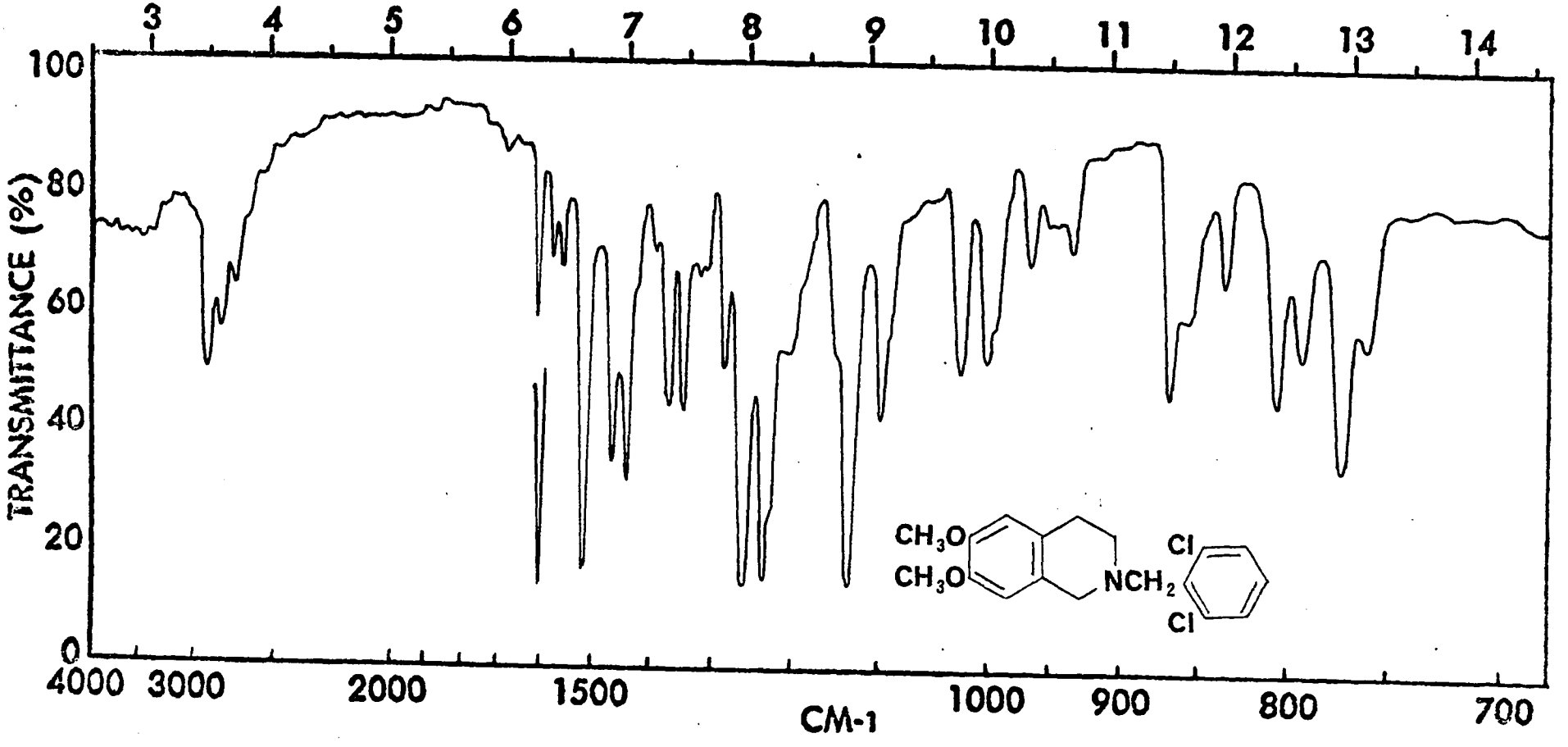
A-7. 2-(2',6'-Dichlorobenzyl)-1,2,3,4-tetrahydroisoquinoline (40).



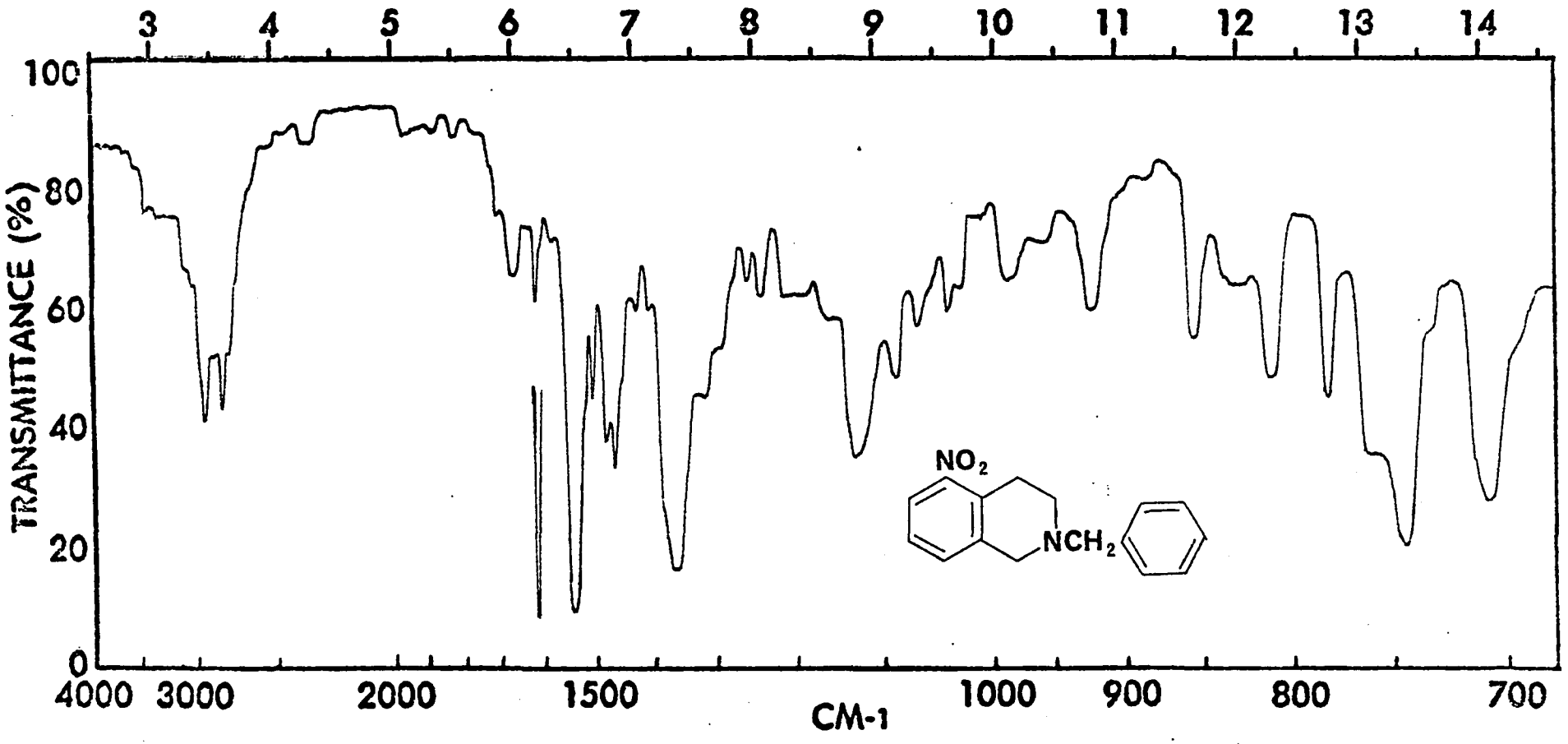
A-8. 2-(4'-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (43).



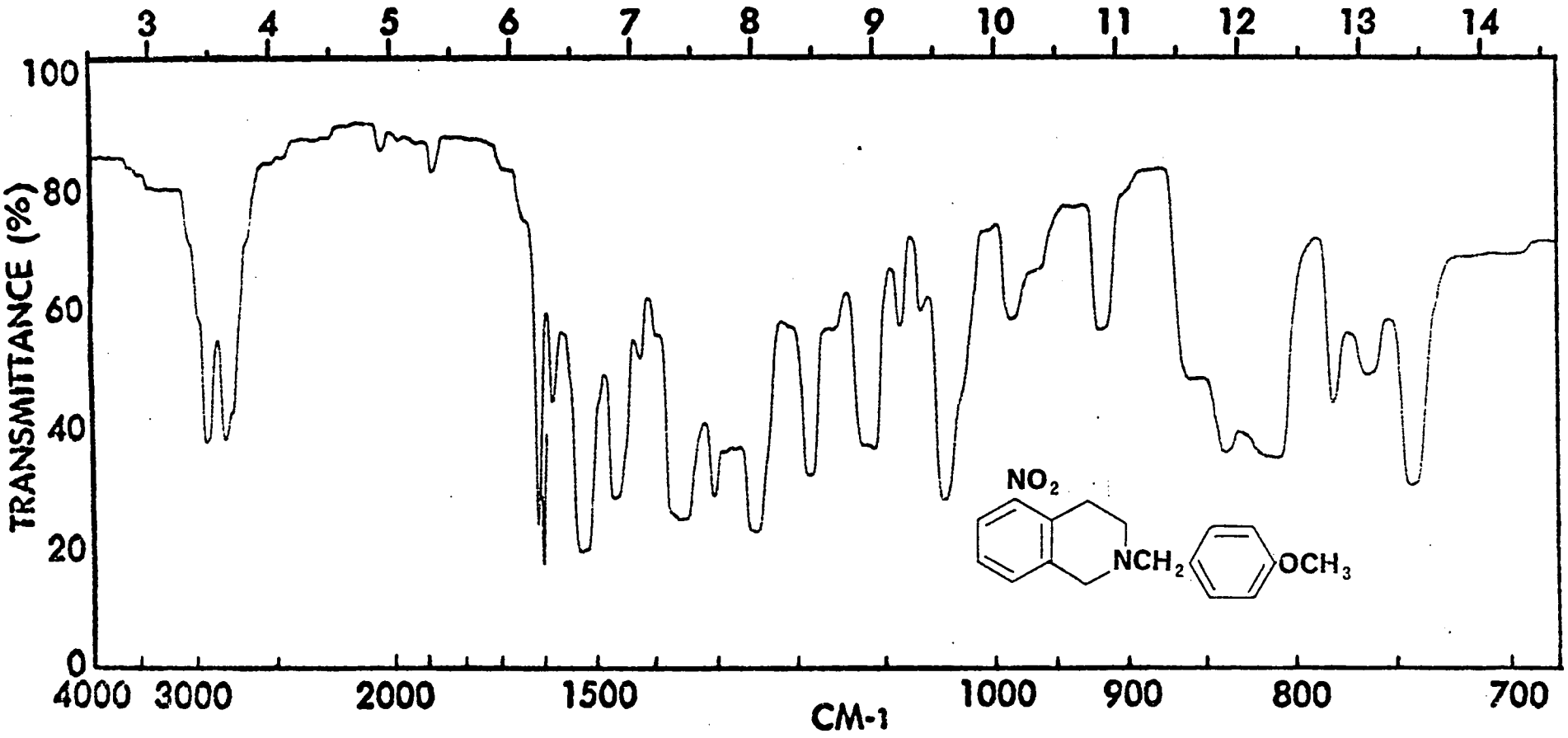
A-9. 2-(3',4'-Dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (<u>44</u>).



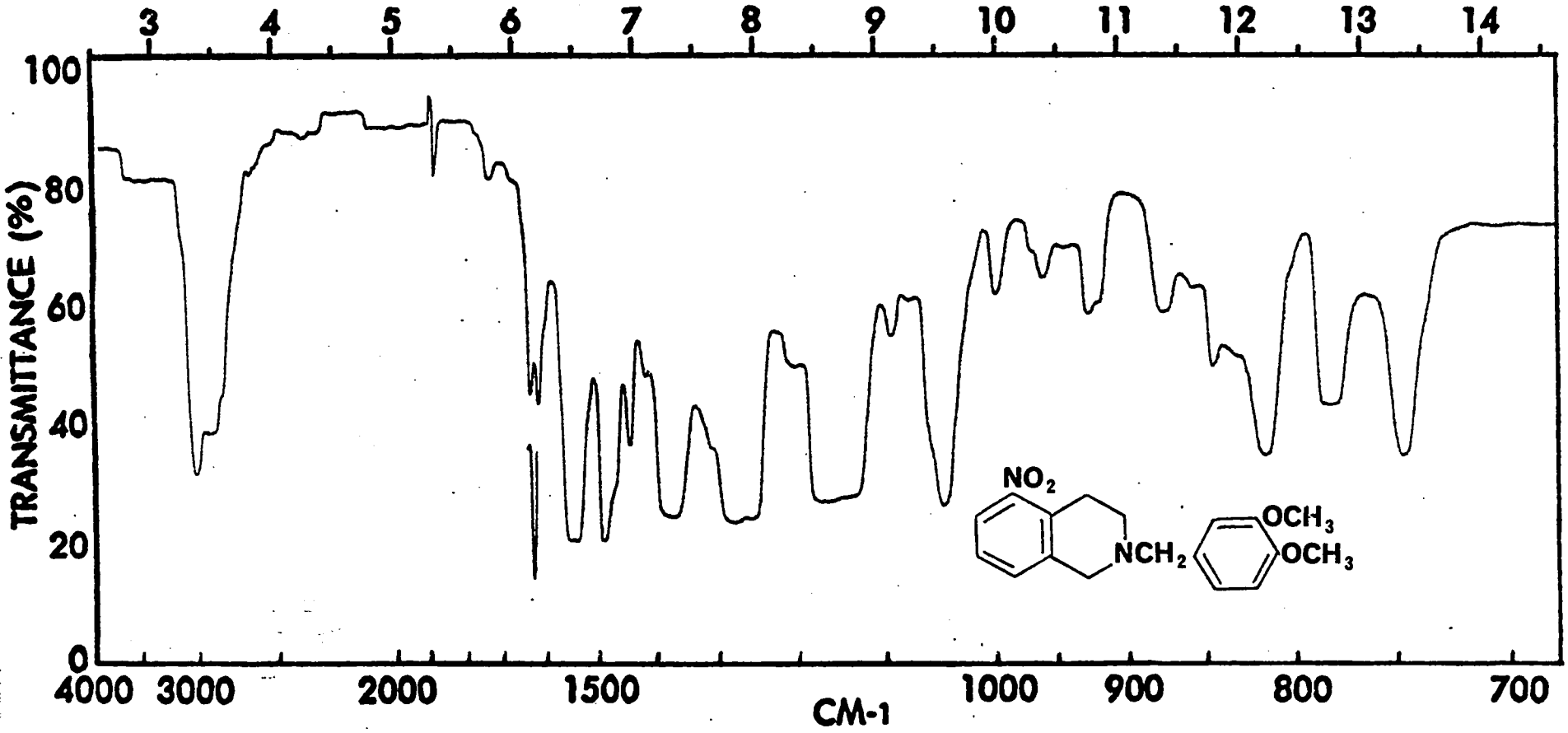
A-10. 2-(2',6'-Dichlorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (49).



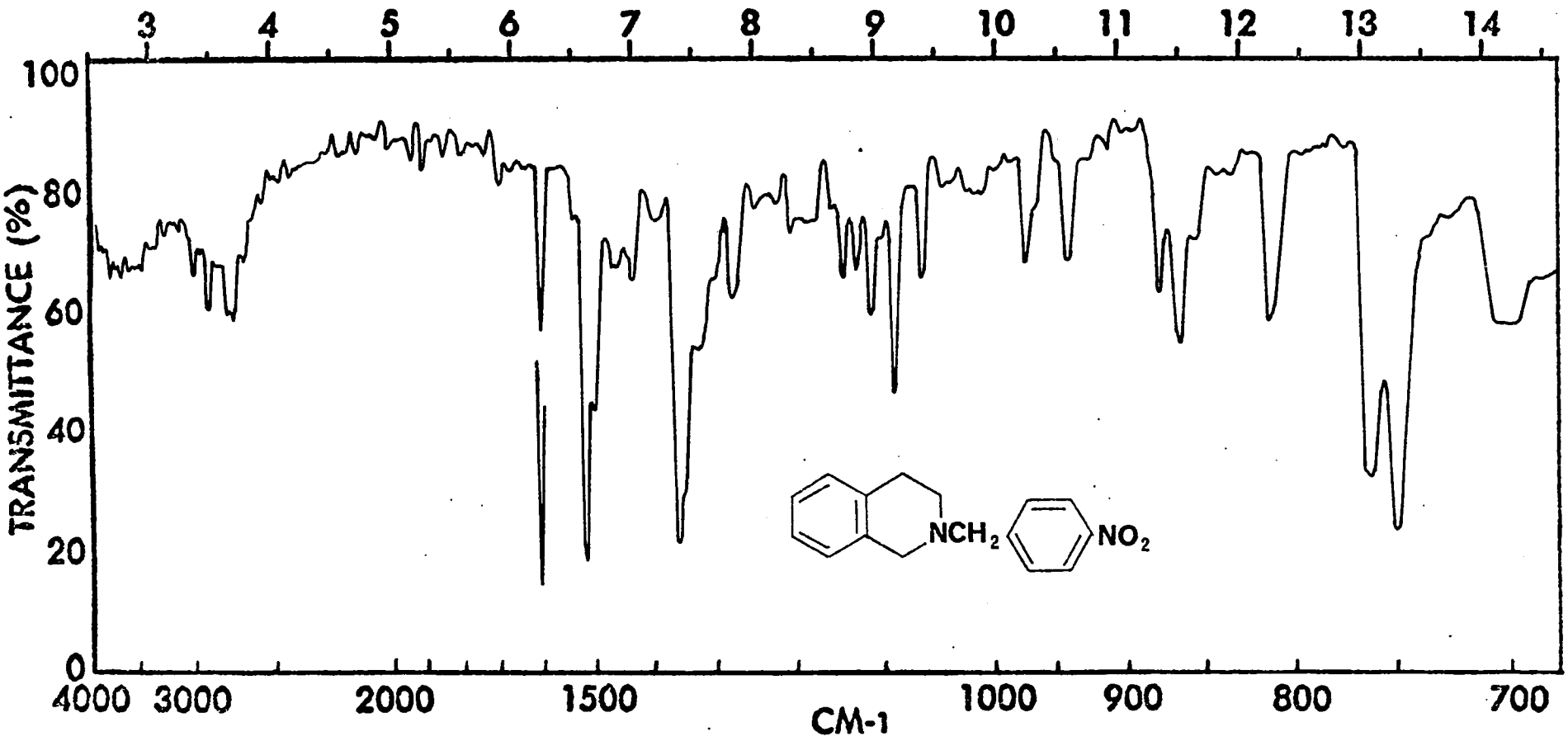
A-11. 2-Benzyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (54).



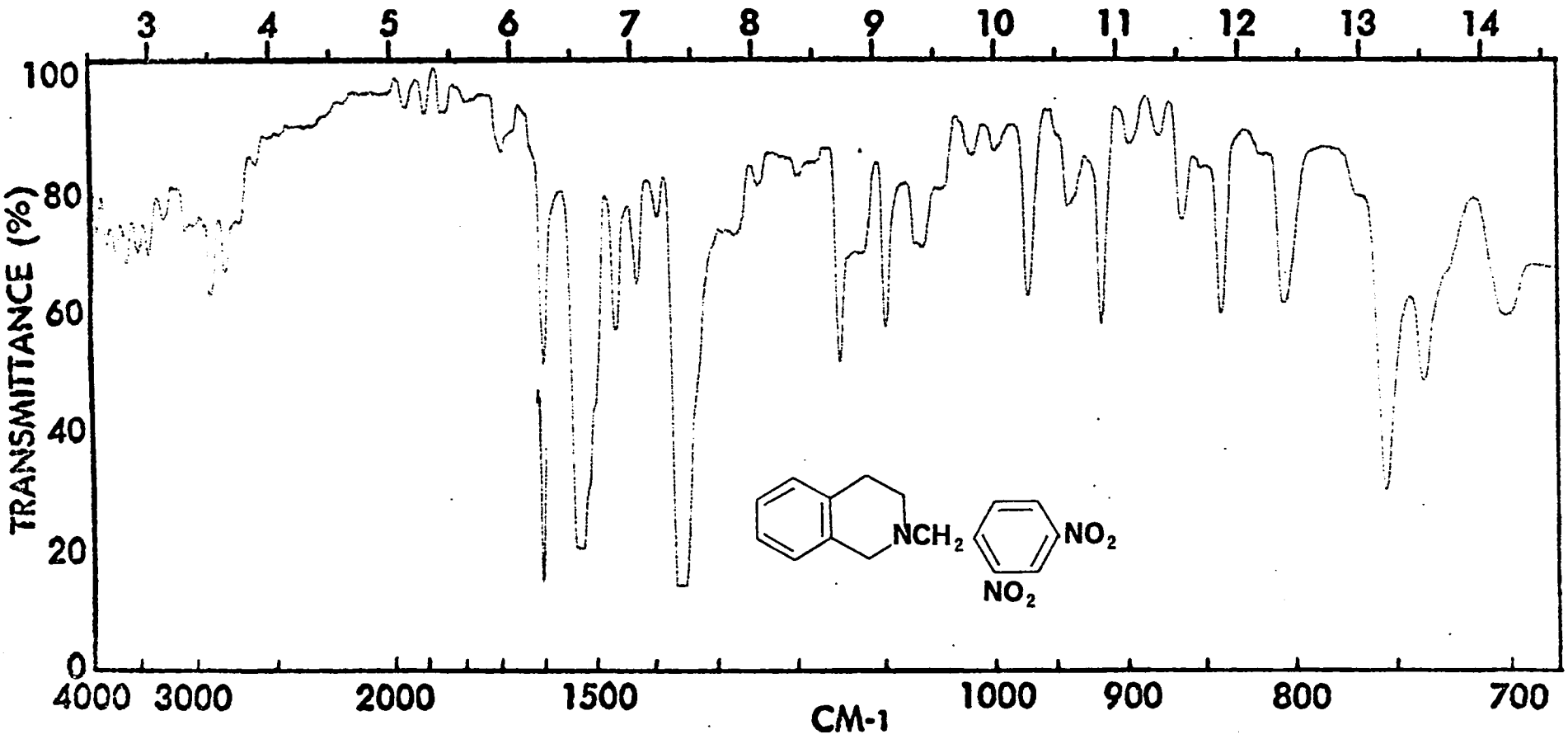
A-12. 2-(4'-Methoxybenzyl)-5-nitro-1,2,3,4-tetrahydroisoquinoline (55).



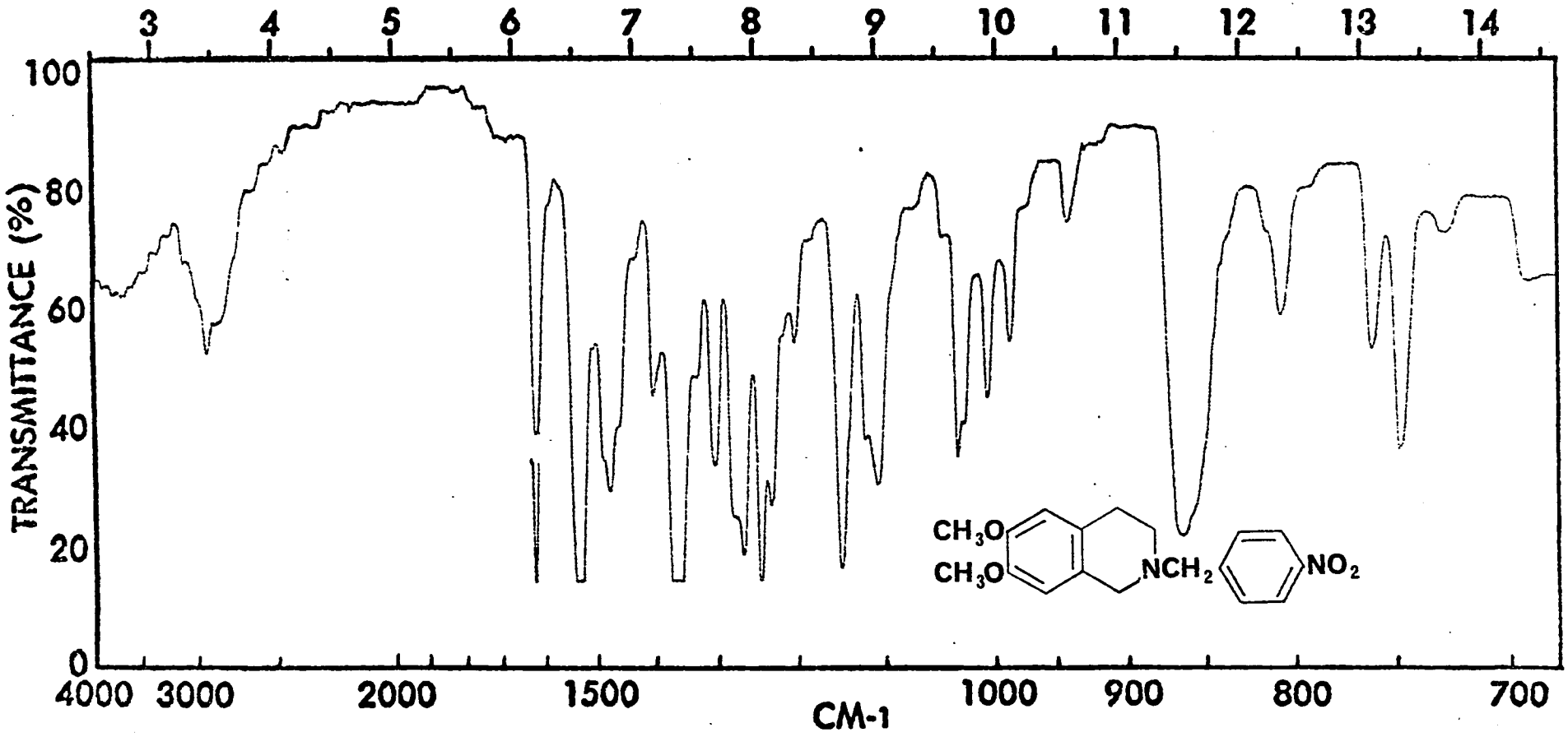
A-13. 2-(3',4'-Dimethoxybenzyl)-5-nitro-1,2,3,4-tetrahydroisoquinoline (56).



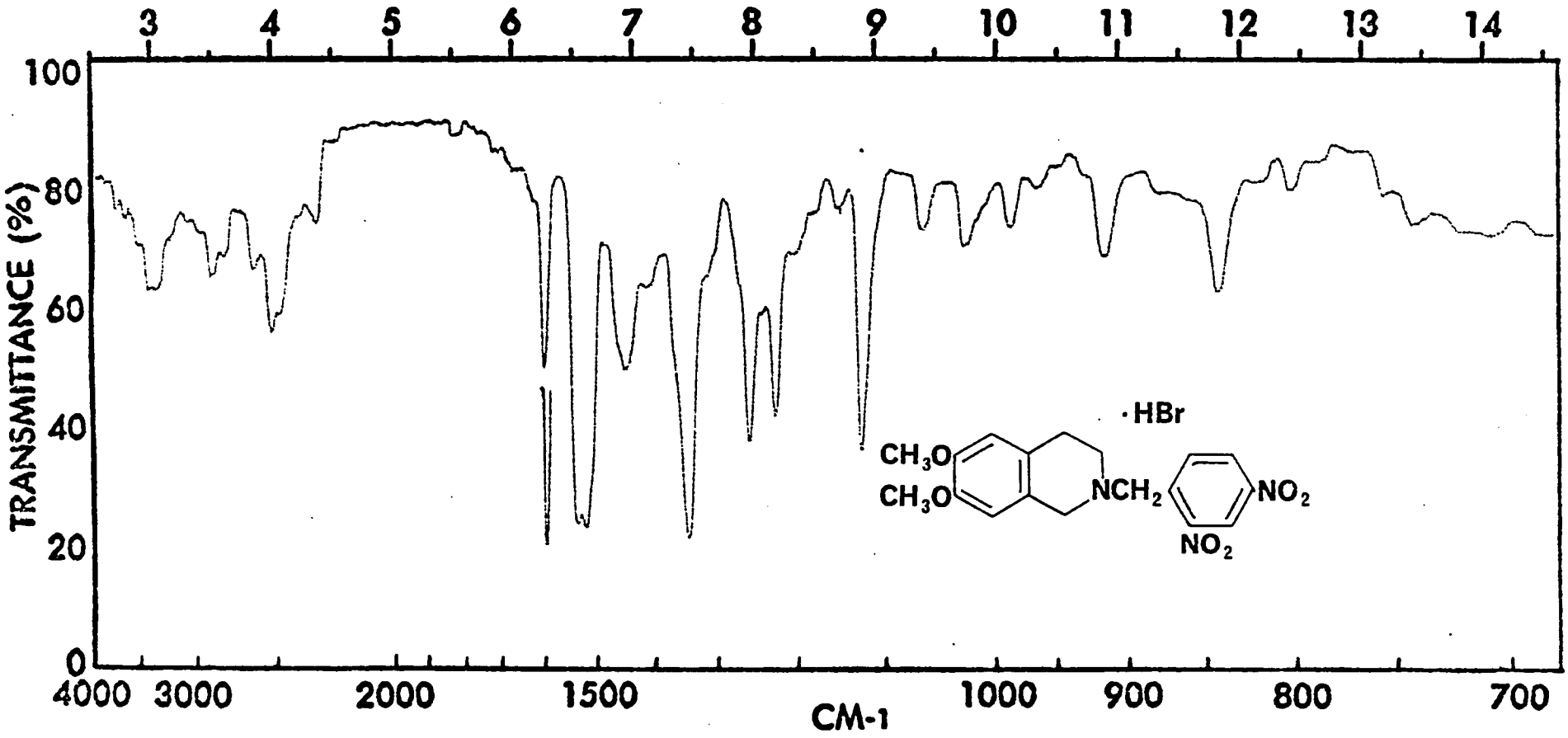
A-14. 2-(4'-Nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (41).



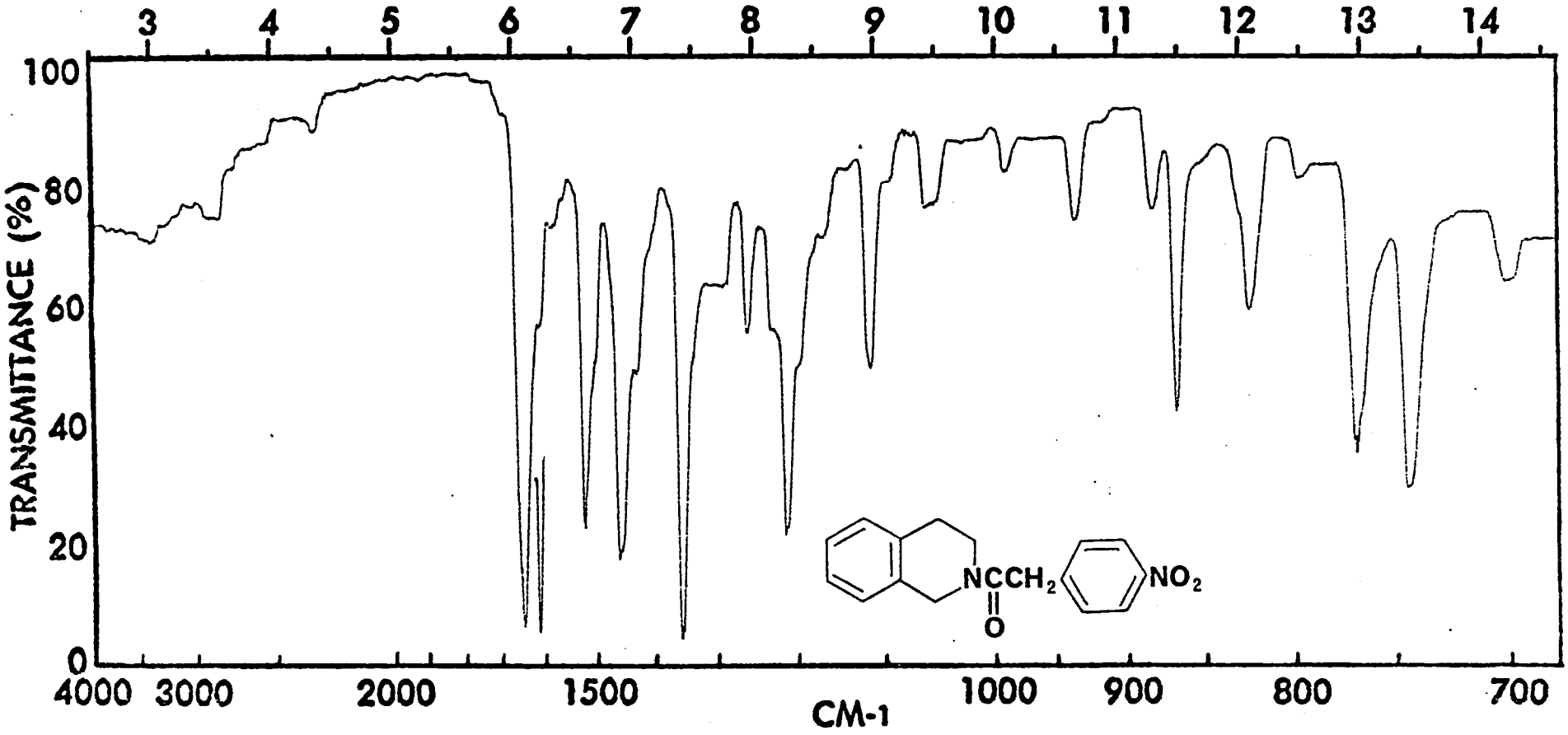
A-15. 2-(2',4'-Dinitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (42).



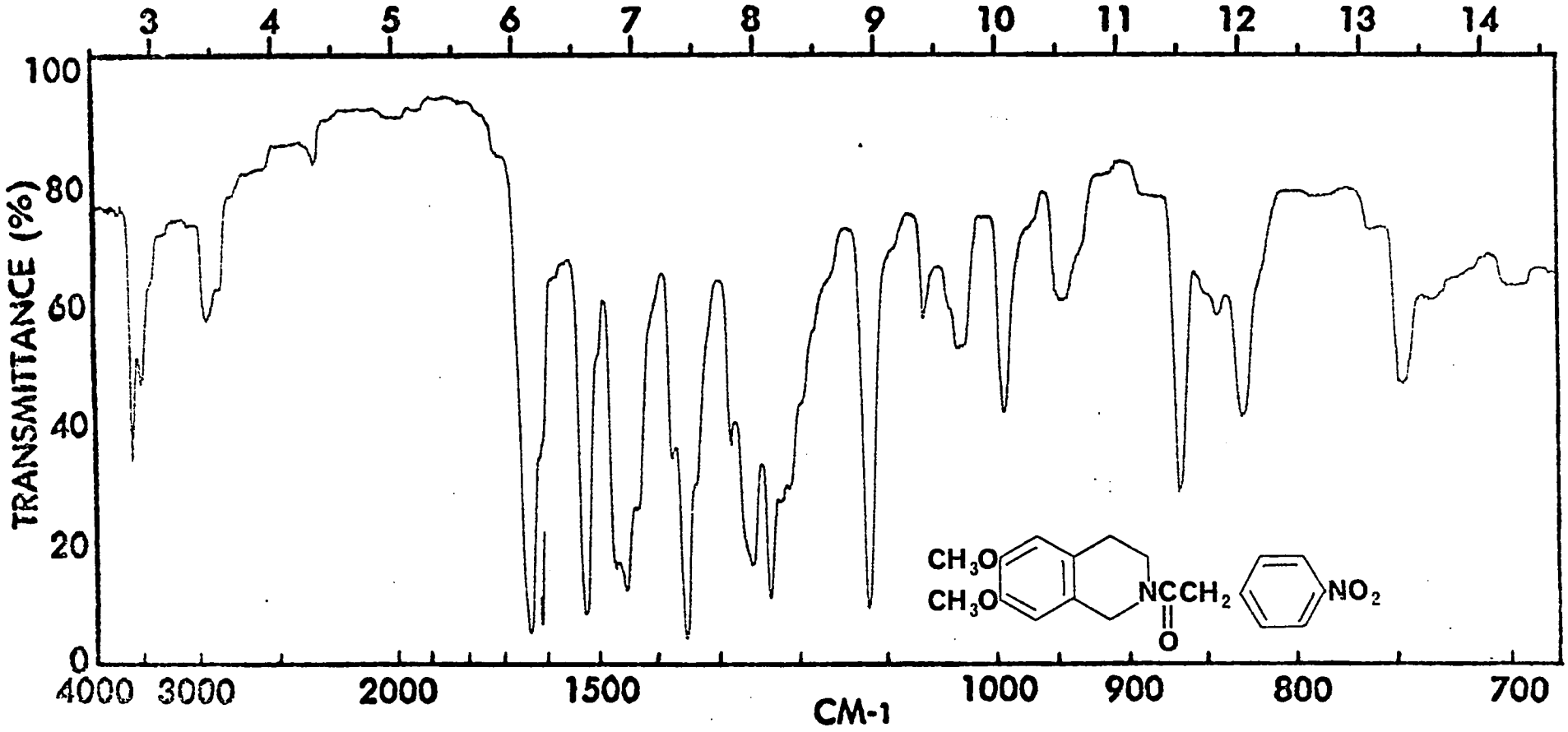
A-16. 2-(4'-Nitrobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (50).



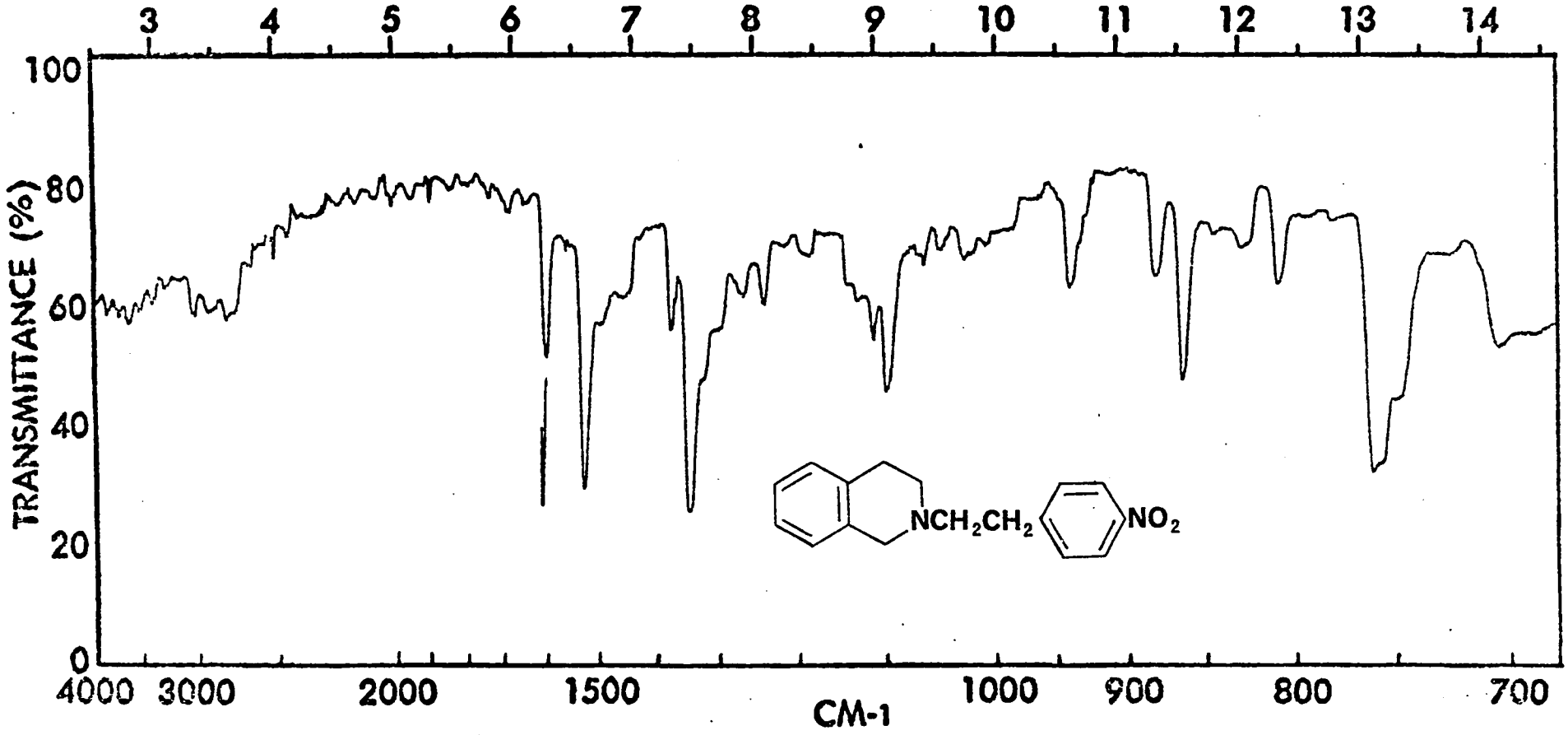
A-17. 2-(2',4'-Dinitrobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (51).



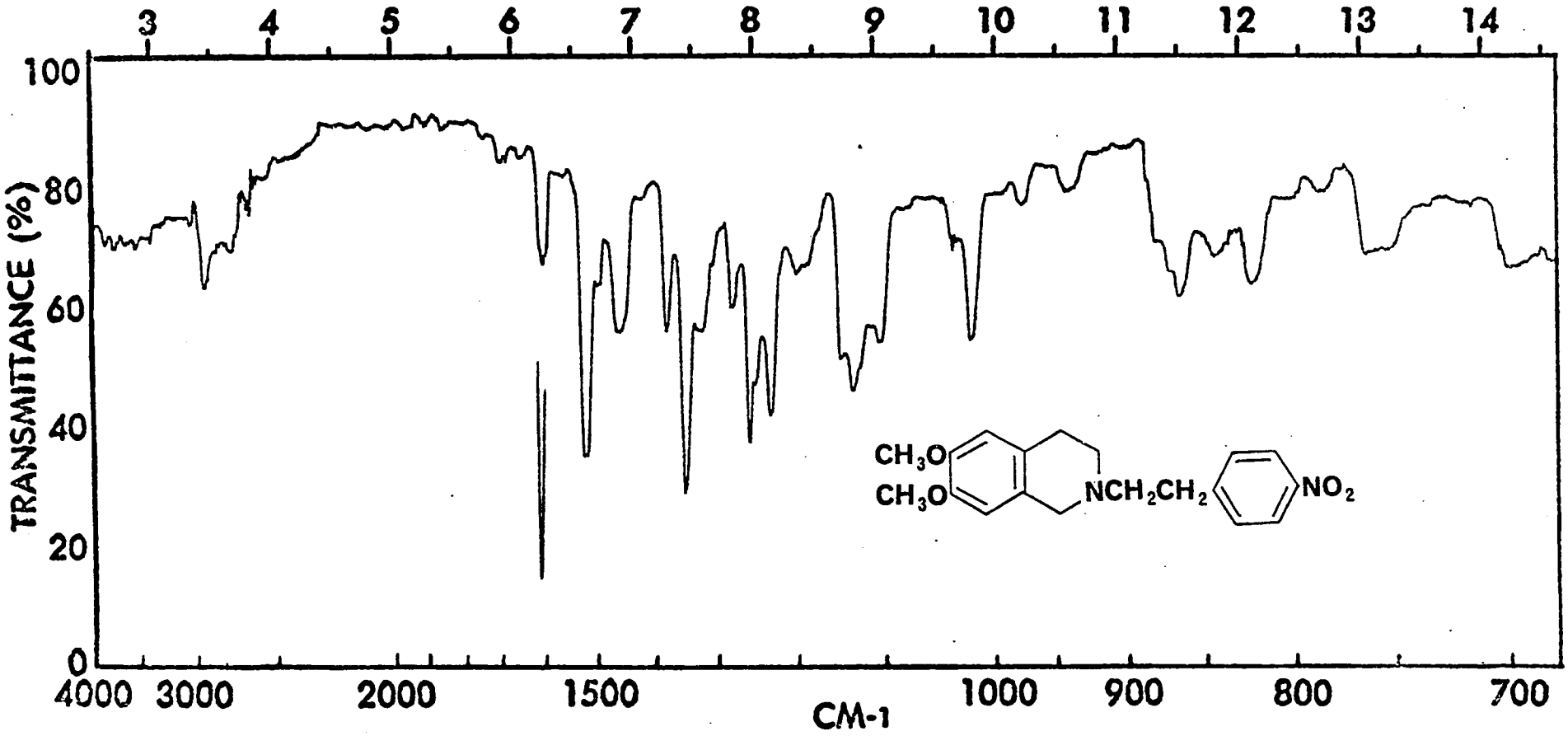
A-18. 2-(4'-Nitrophenacetyl)-1,2,3,4-tetrahydroisoquinoline (59).



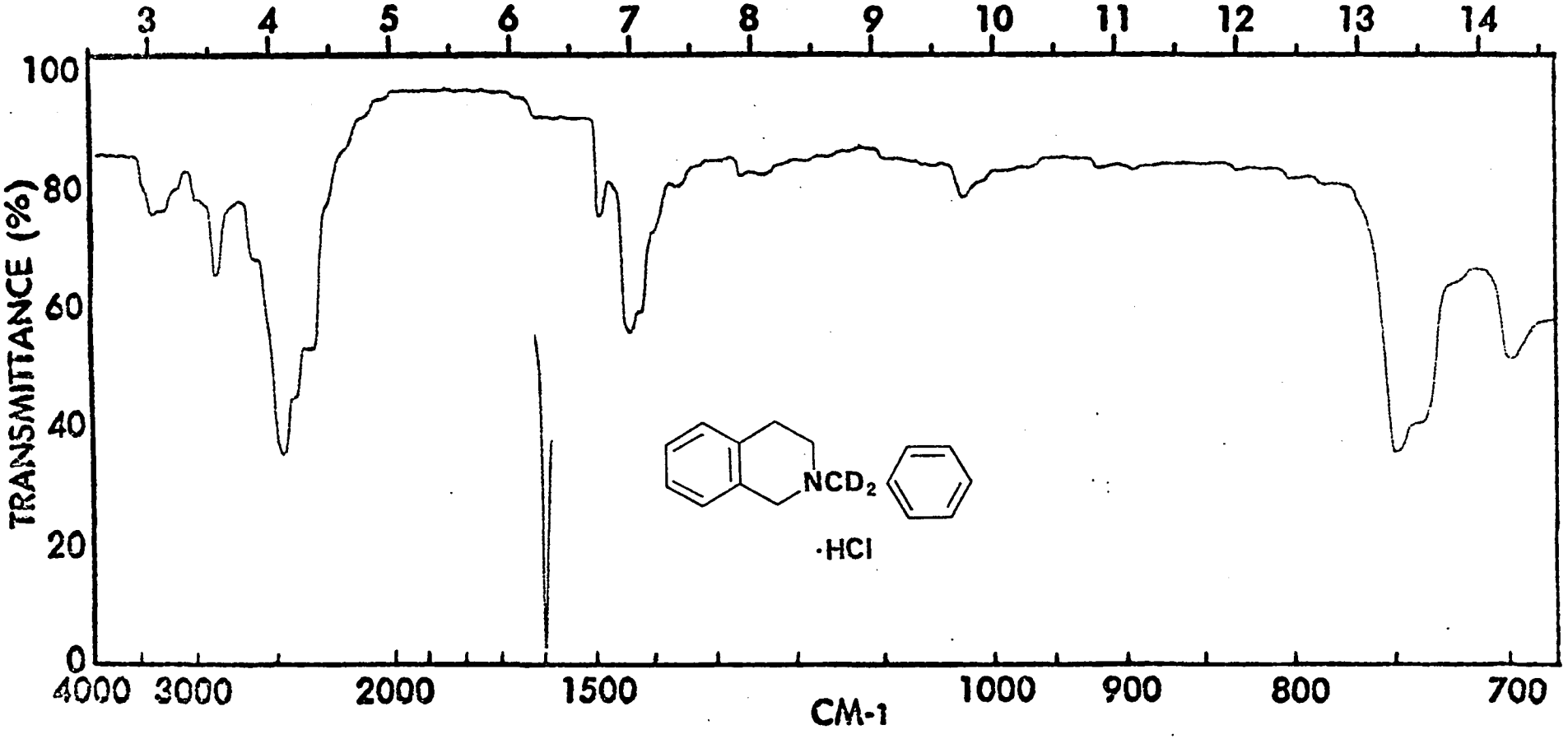
A-19. 2-(4'-Nitrophenacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (60).



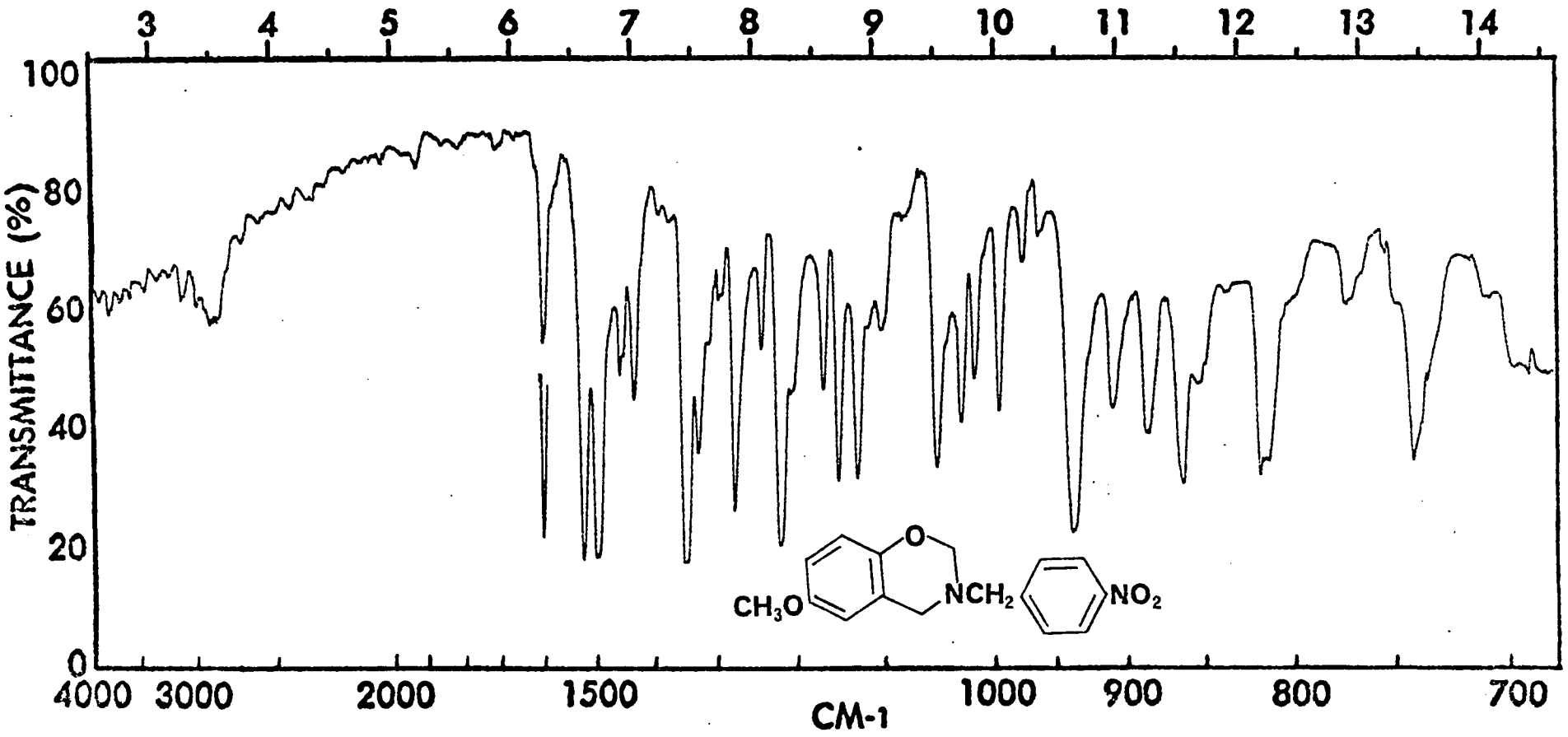
A-20. 2-[β-(4'-Nitrophenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (45).



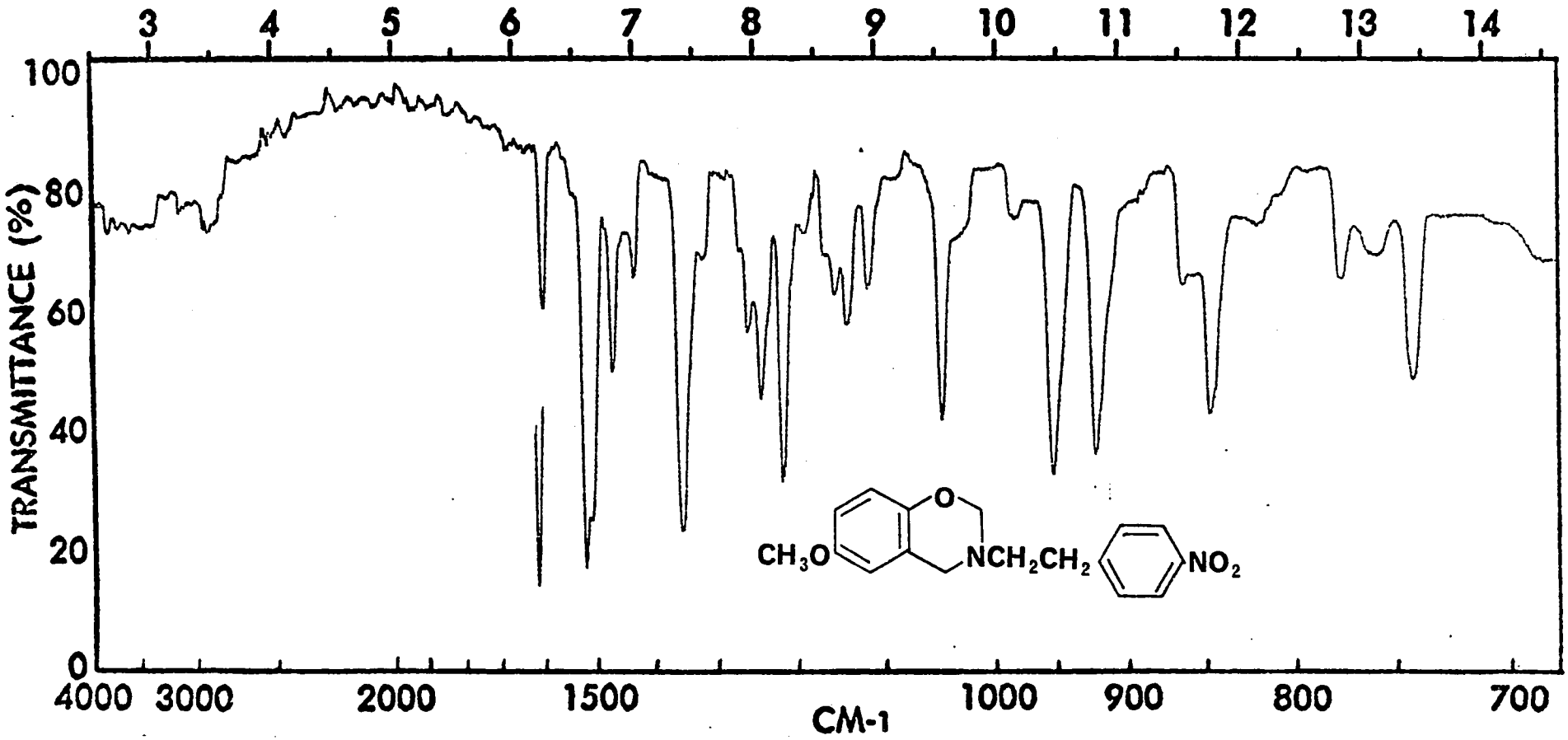
A-21. 2-[β-(4'-Nitrophenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (52).



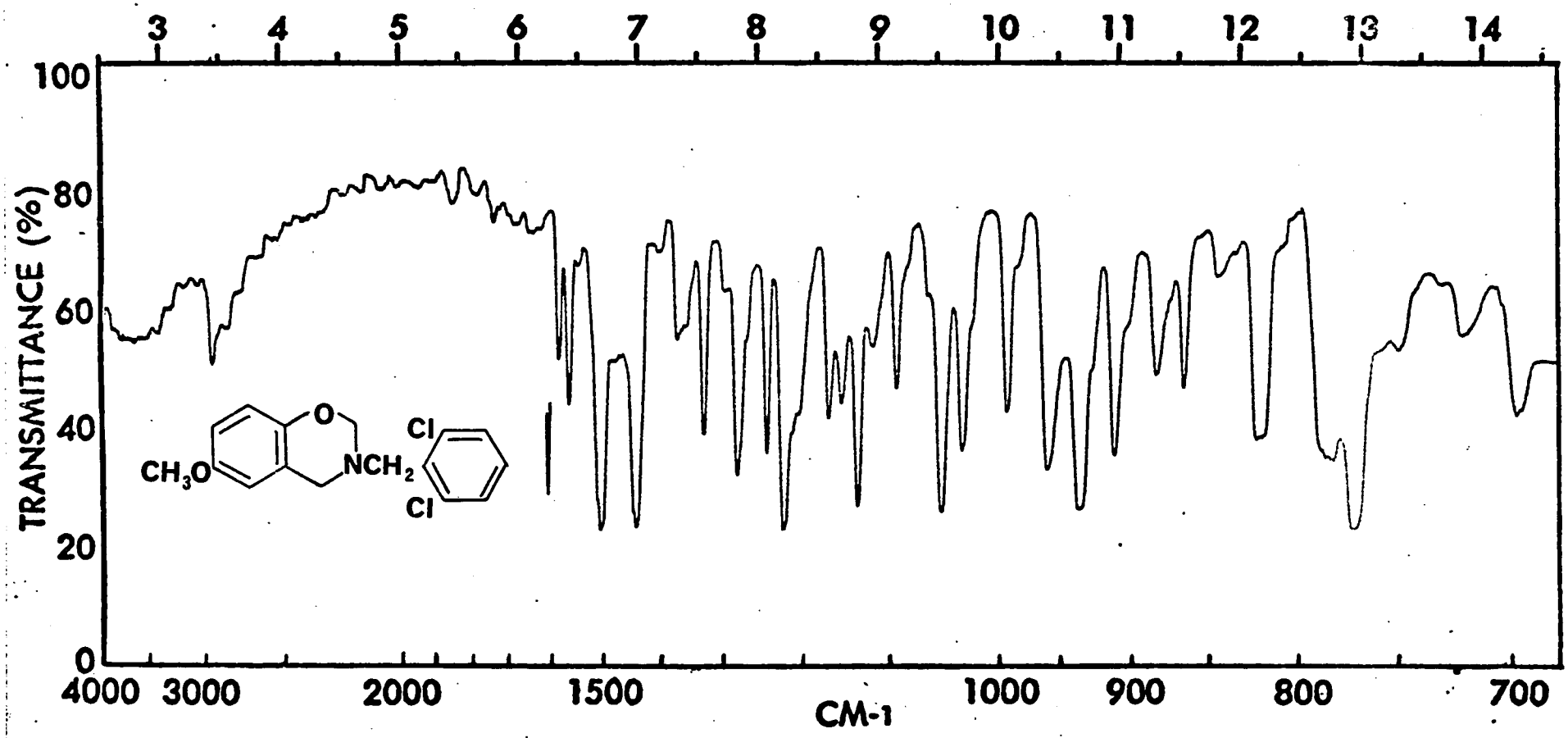
A-22. α,α-Dideutero-2-benzyl-1,2,3,4-tetrahydroisoquinolinium Hydrochloride (61).



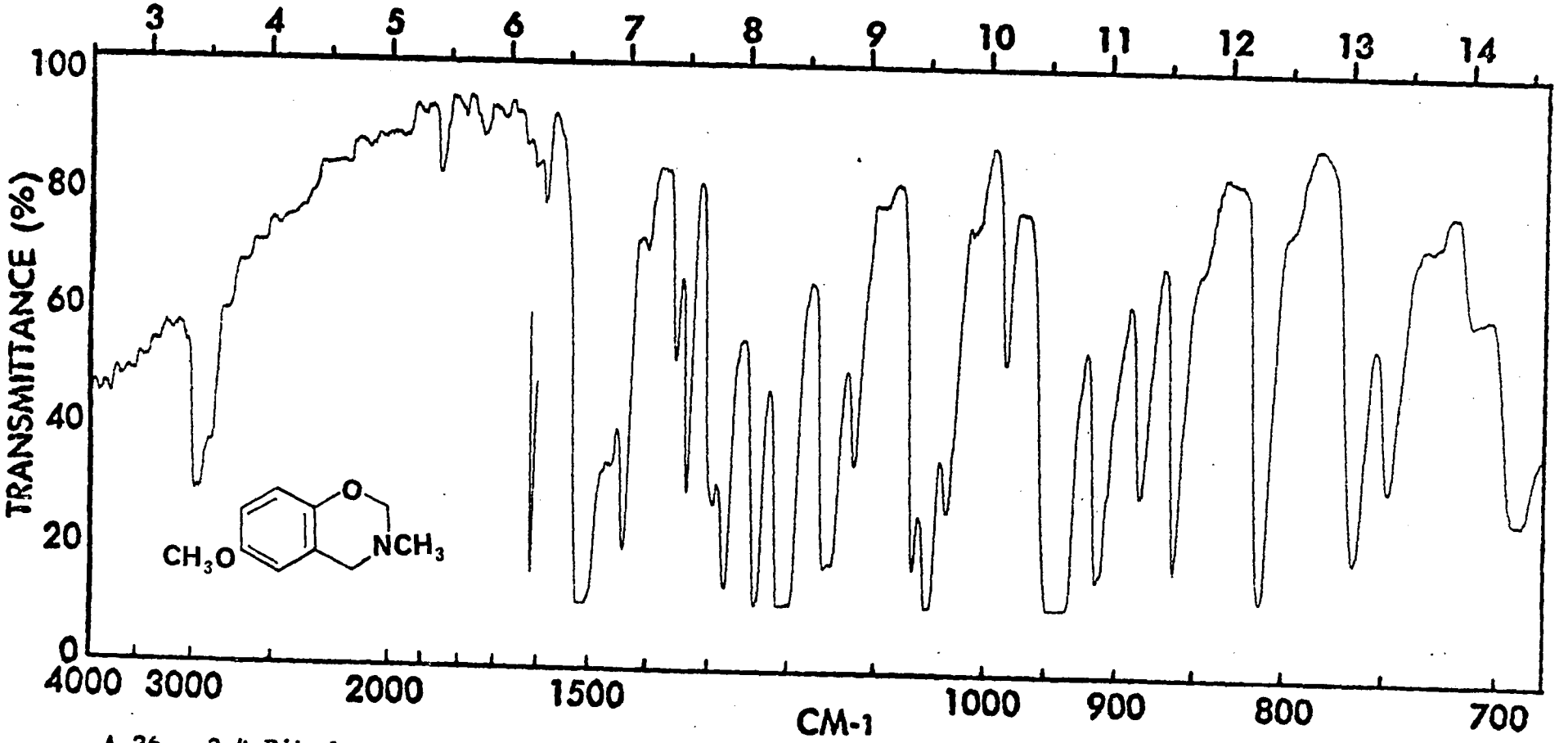
A-23. 3,4-Dihydro-3-(4'-nitrobenzyl)-6-methoxy-1,3,2H-benzoxazine (71).



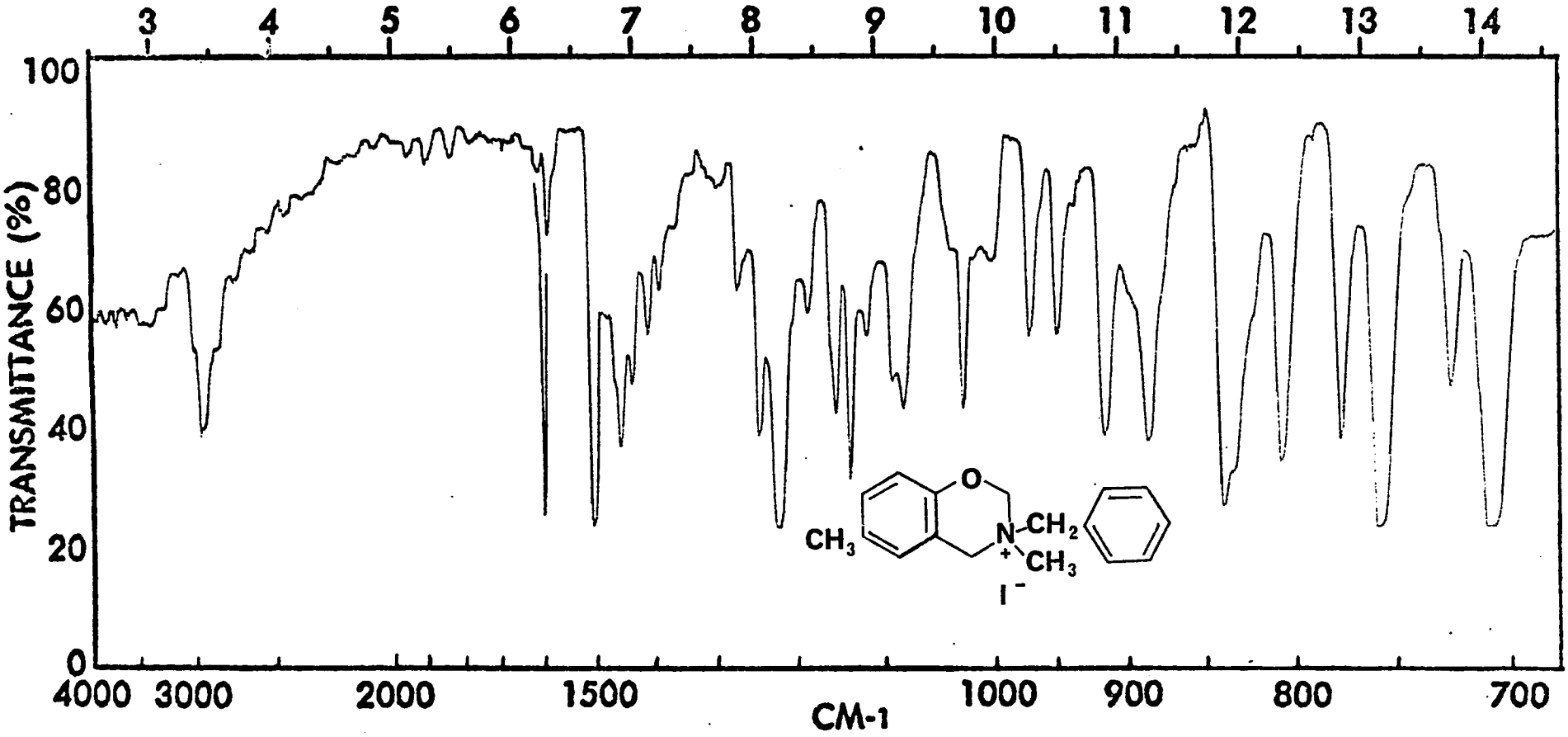
A-24. 3,4-Dihydro-3-[β-(4'-nitrophenyl)ethyl]-6-methoxy-1,3,2H-benzoxazine (73).



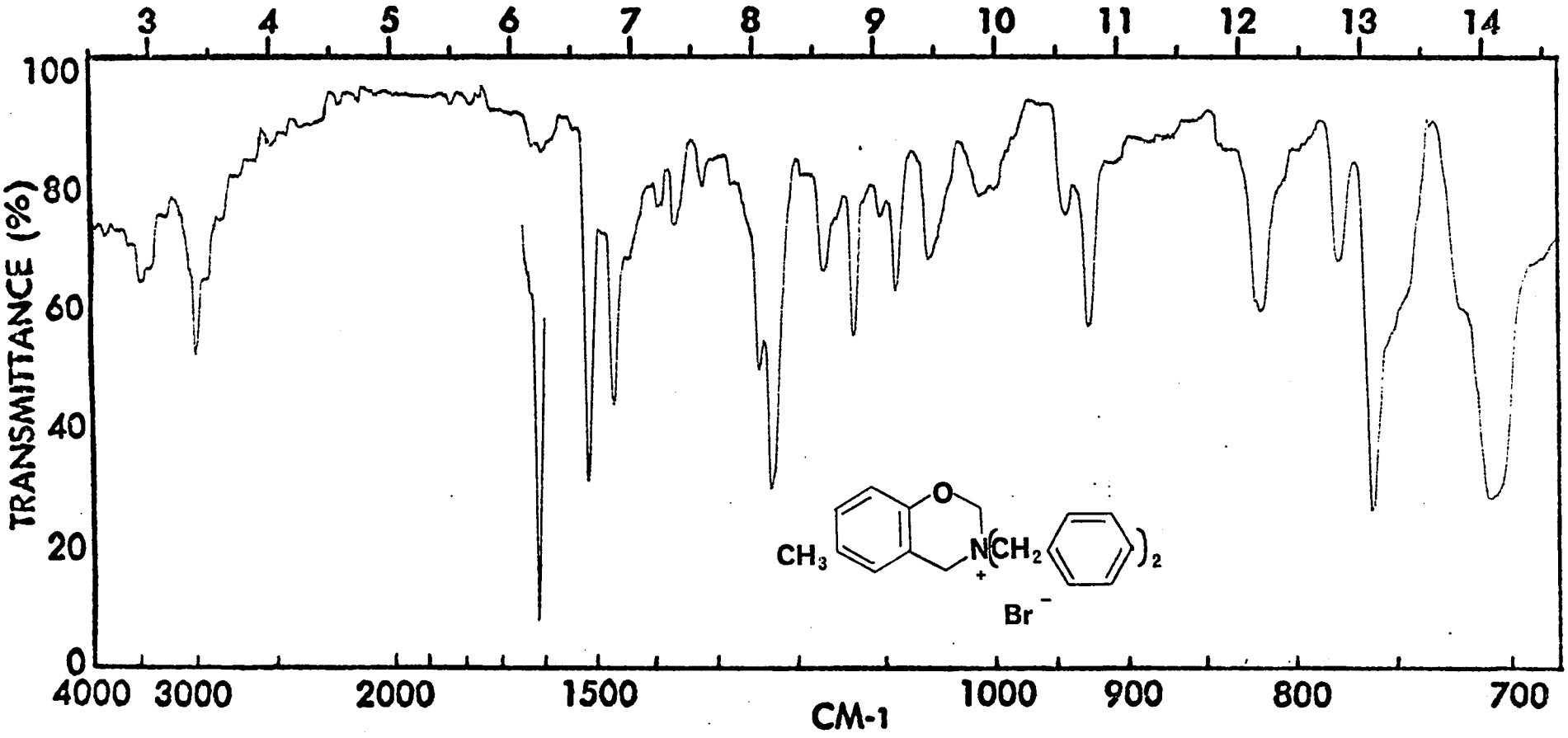
A-25. 3,4-Dihydro-3-(2',6'-dichlorobenzyl)-6-methoxy-1,3,2H-benzoxazine (74).



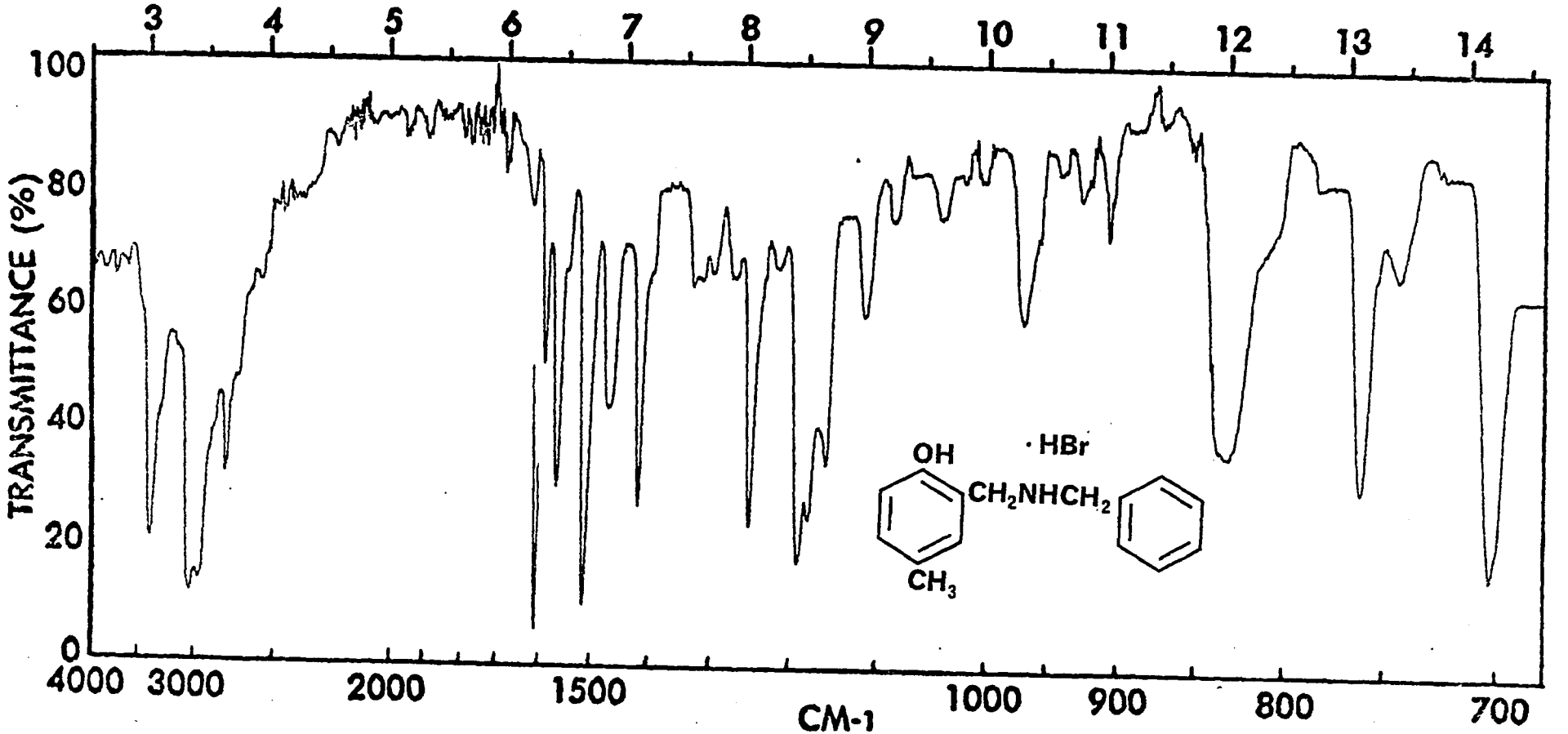
A-26. 3,4-Dihydro-3-methyl-6-methoxy-1,3,2H-benzoxazine (69).



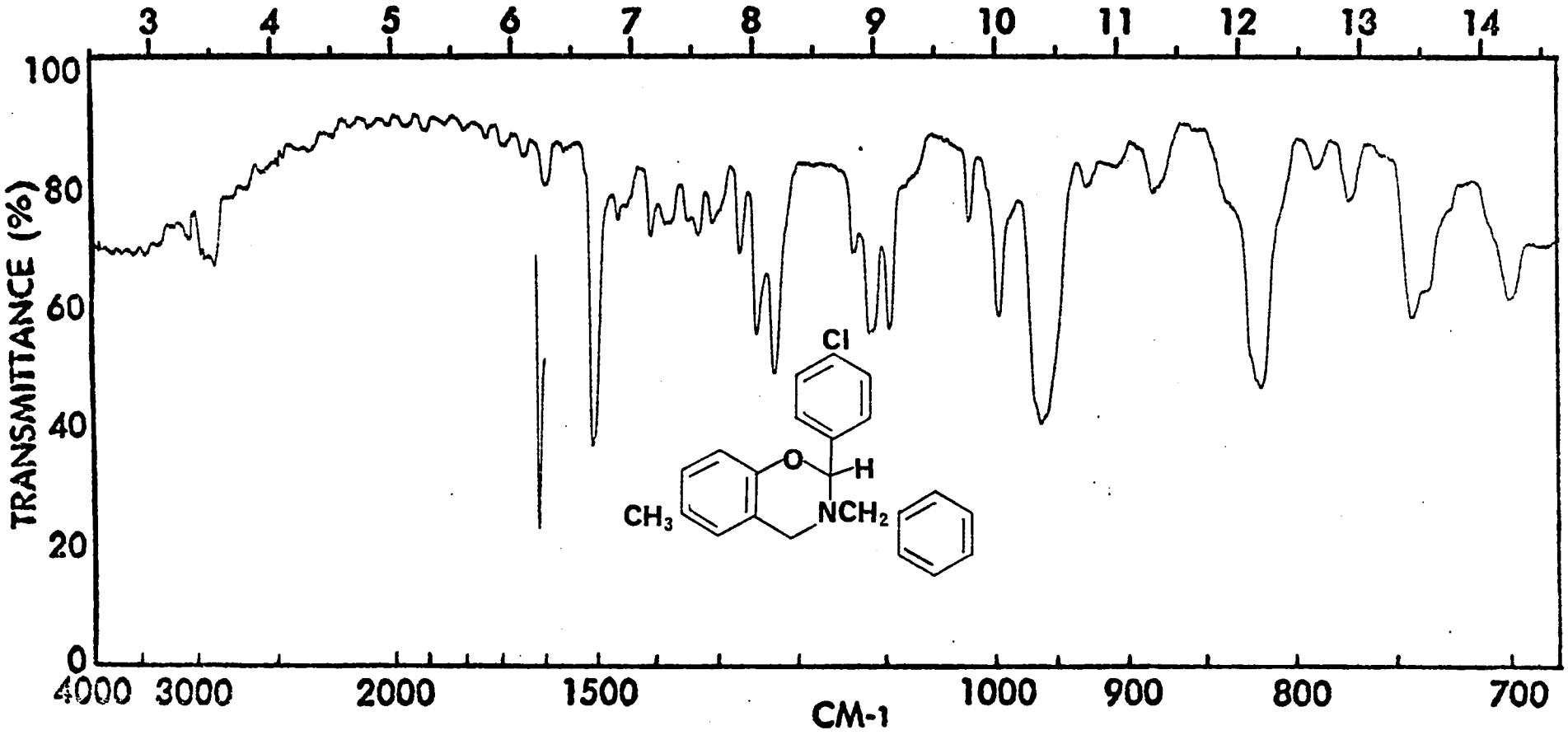
A-27. 3,4-Dihydro-3-benzyl-3,6-dimethyl-1,3,2H-benzoxazinium Iodide (78).



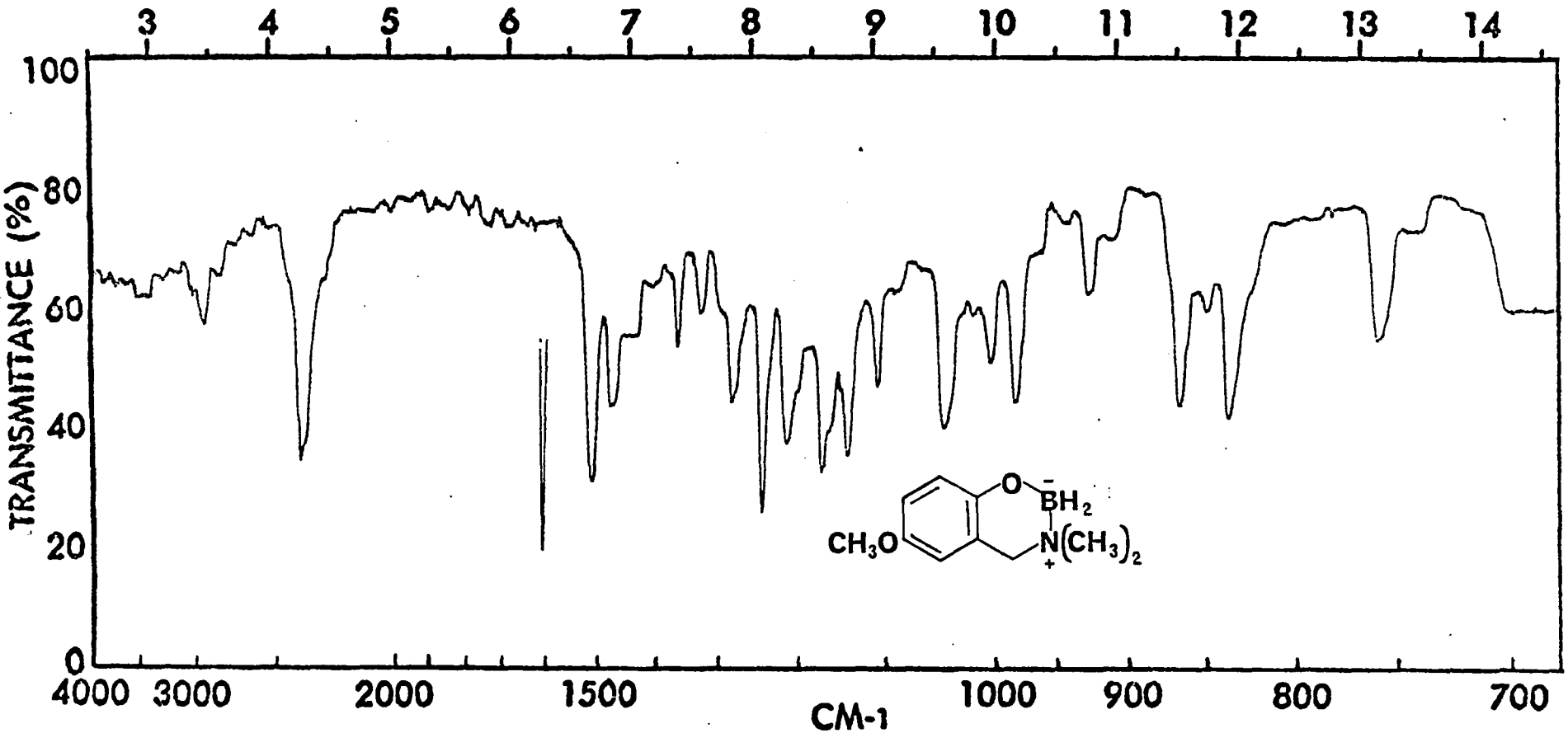
A-28. 3,4-Dihydro-3,4-dibenzyl-6-methyl-1,3,2H-benzoxazinium Bromide (79).



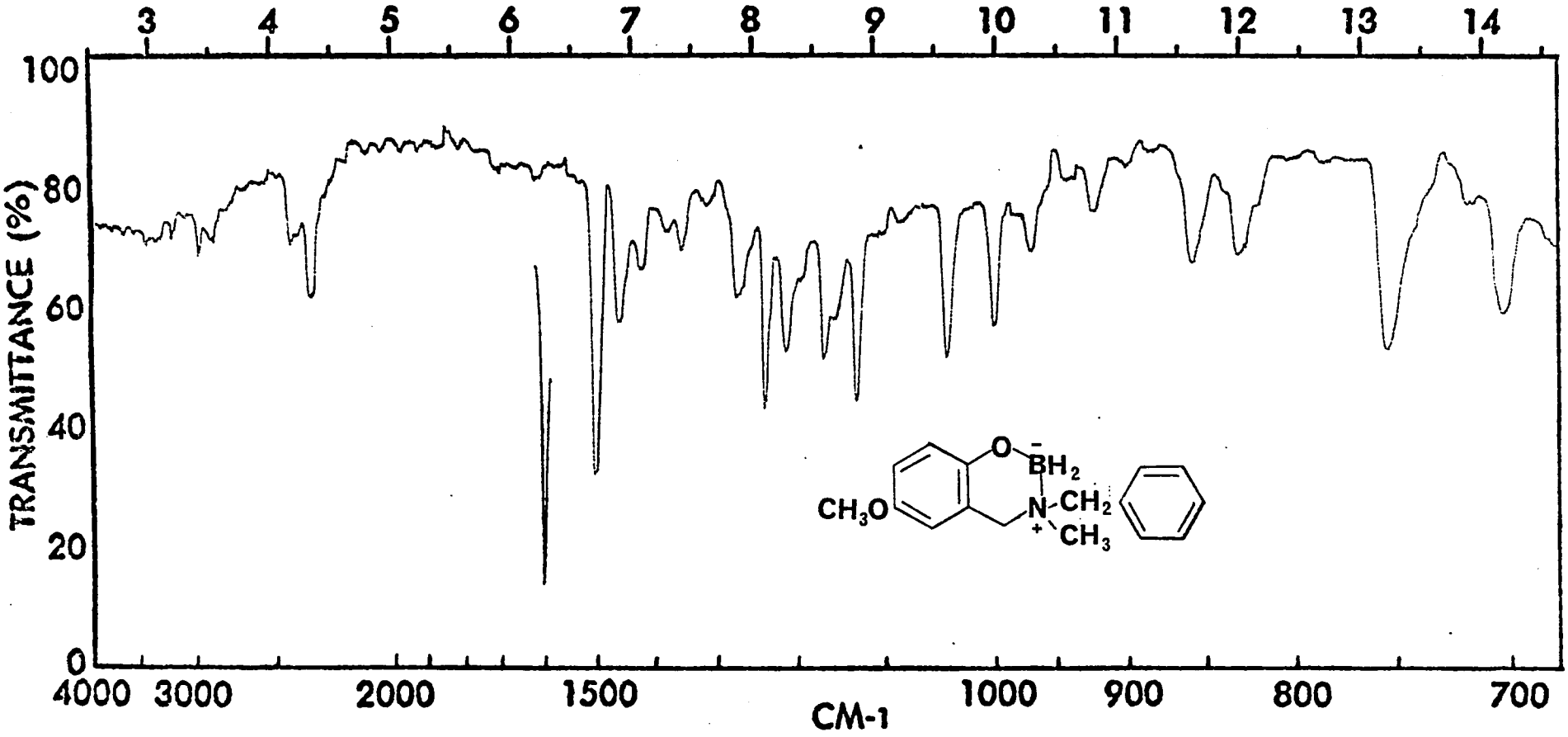
A-29. 2-(Benzylaminomethyl)-4-methylphenol (77).



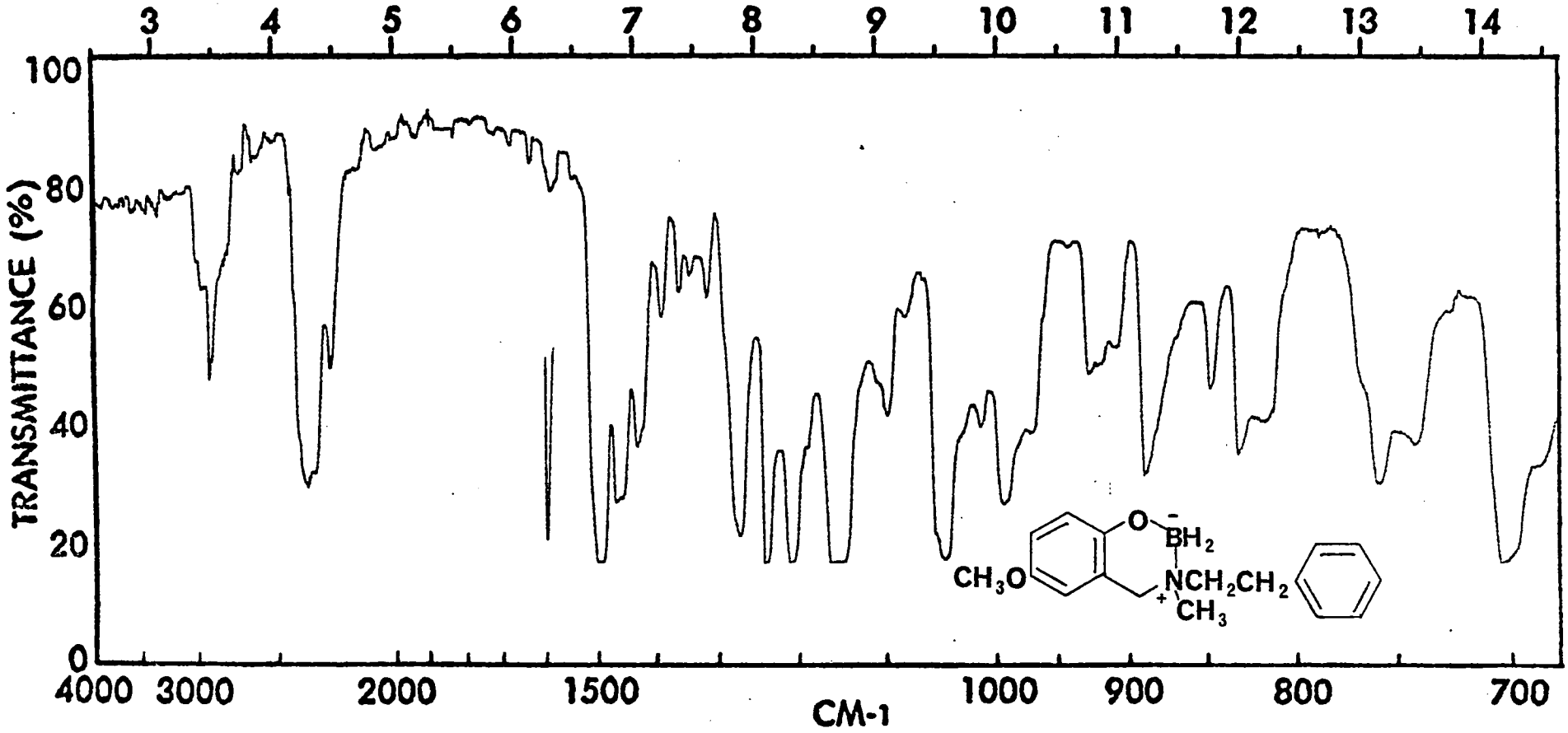
A-30. 3,4-Dihydro-2-p-Chlorophenyl-3-benzyl-6-methyl-1,3,2H-benzoxazine (76).



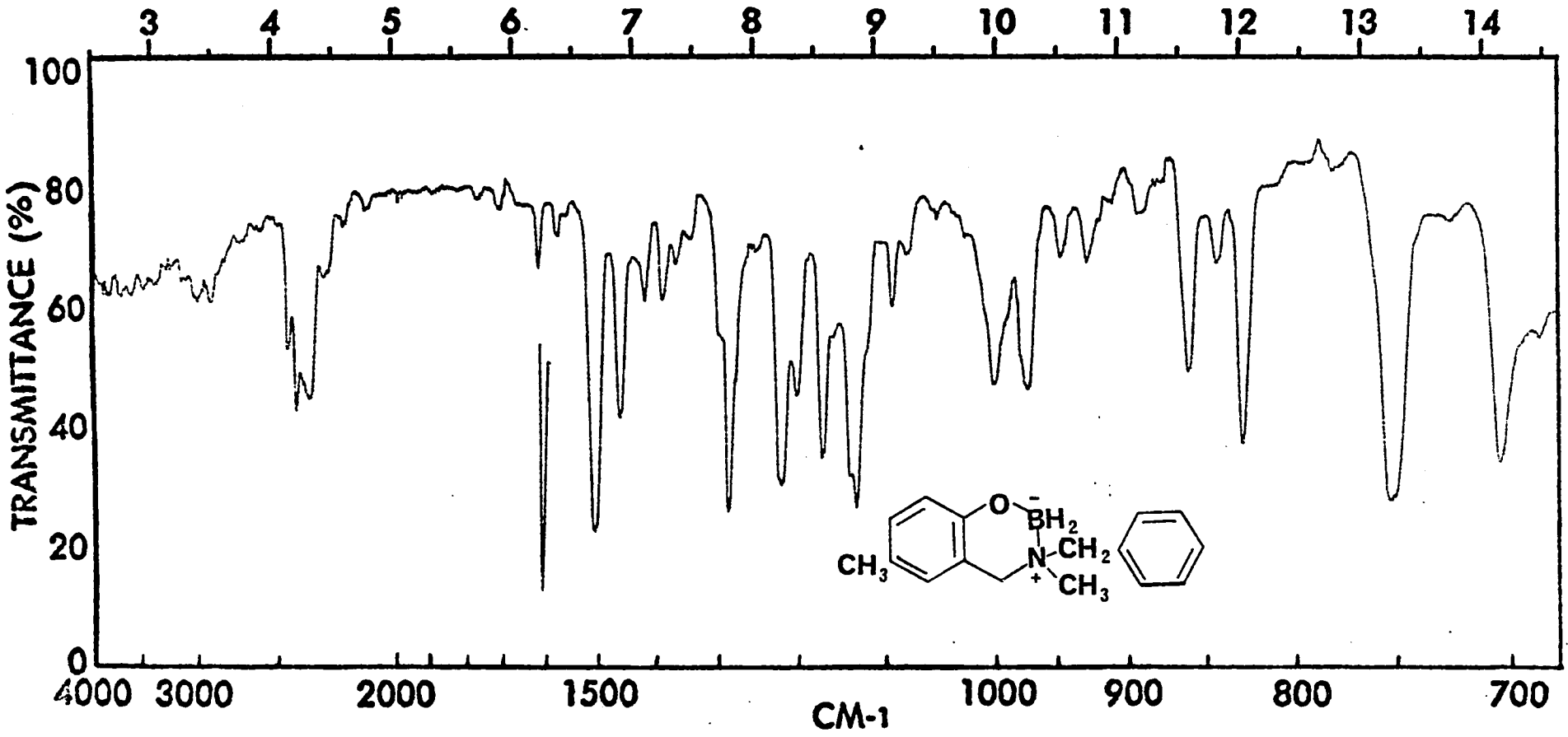
A-31. 3,3-Dimethyl-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (85).



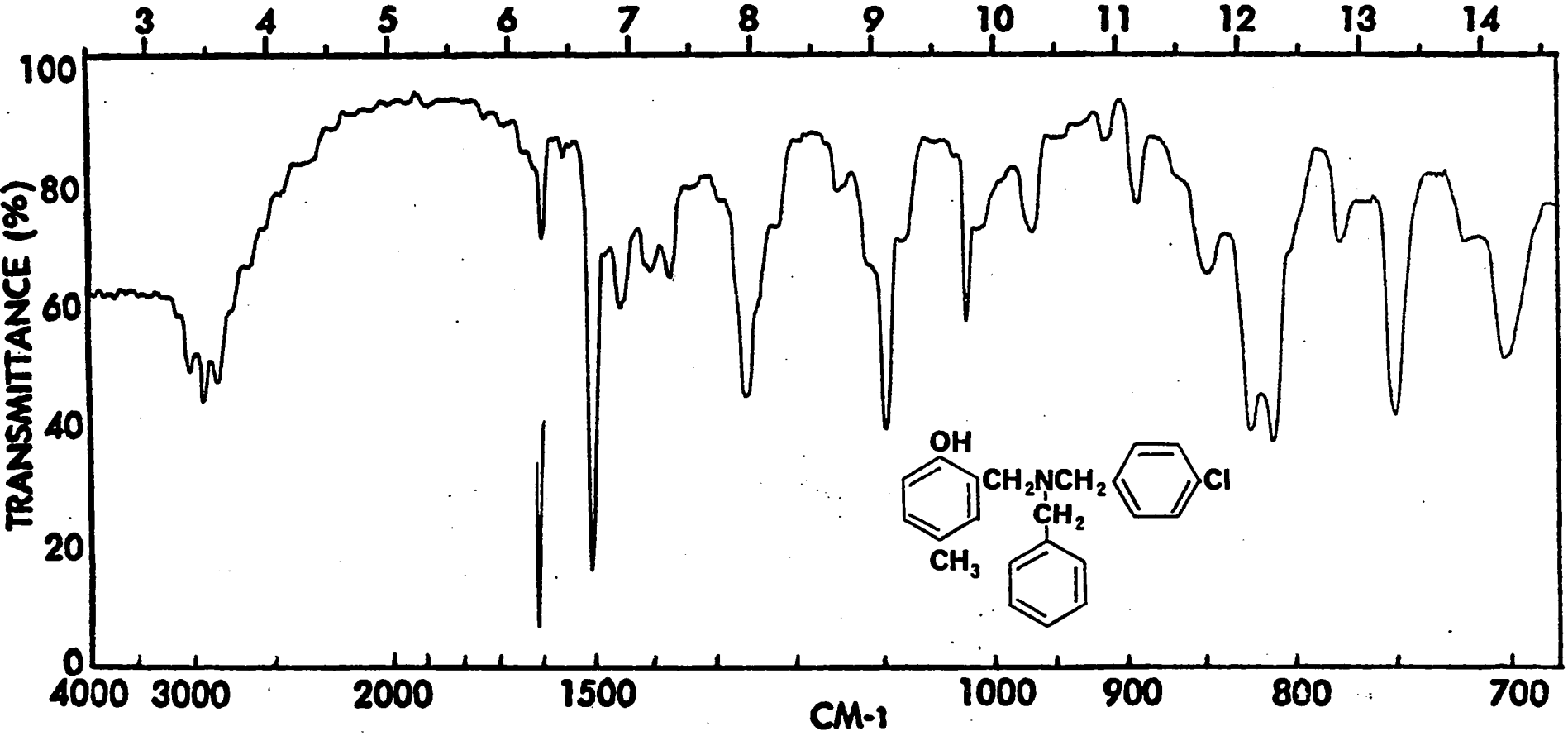
A-32. 3-Benzyl-3-methyl-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (86).



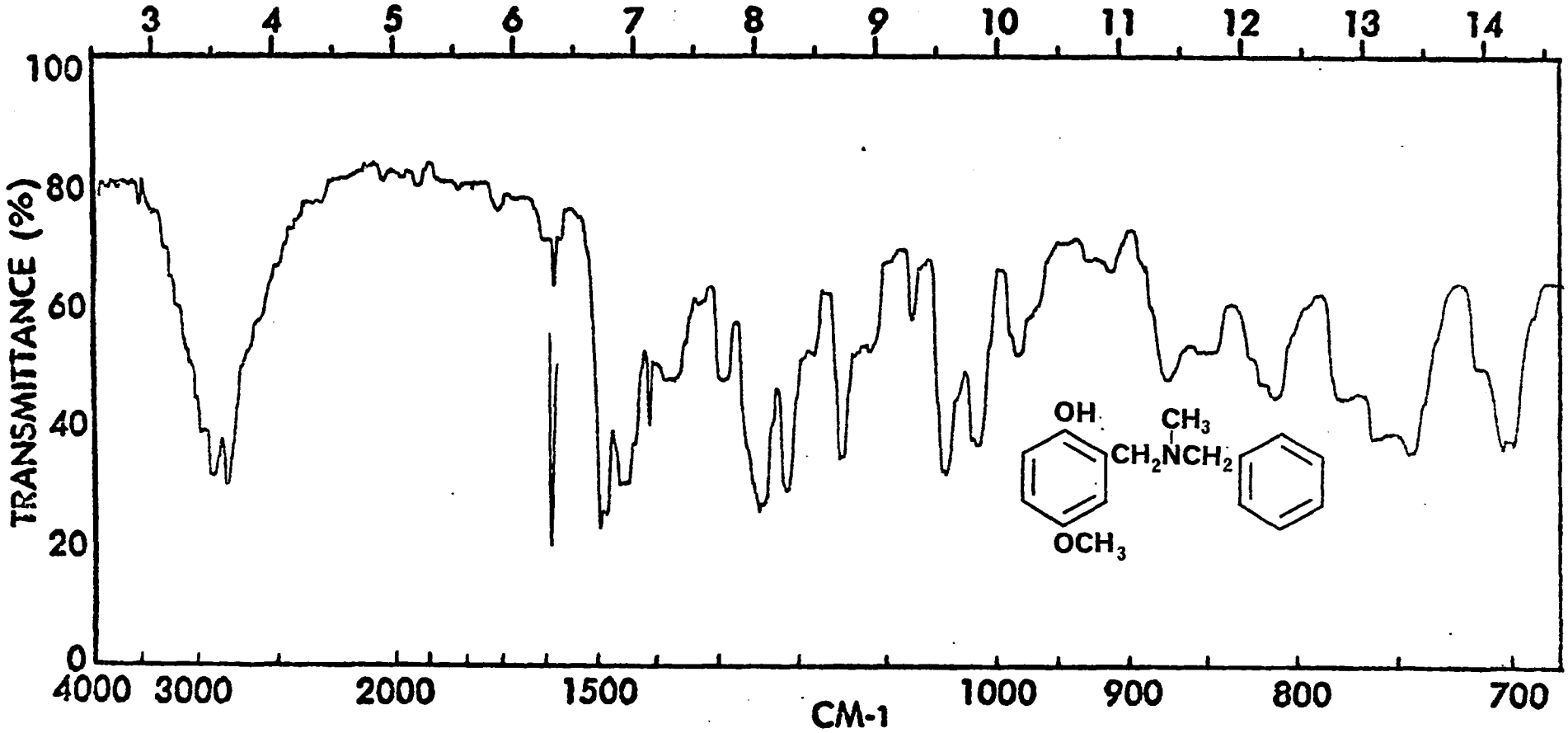
A-33. 3-Methyl-3-(β-phenethyl)-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (87).



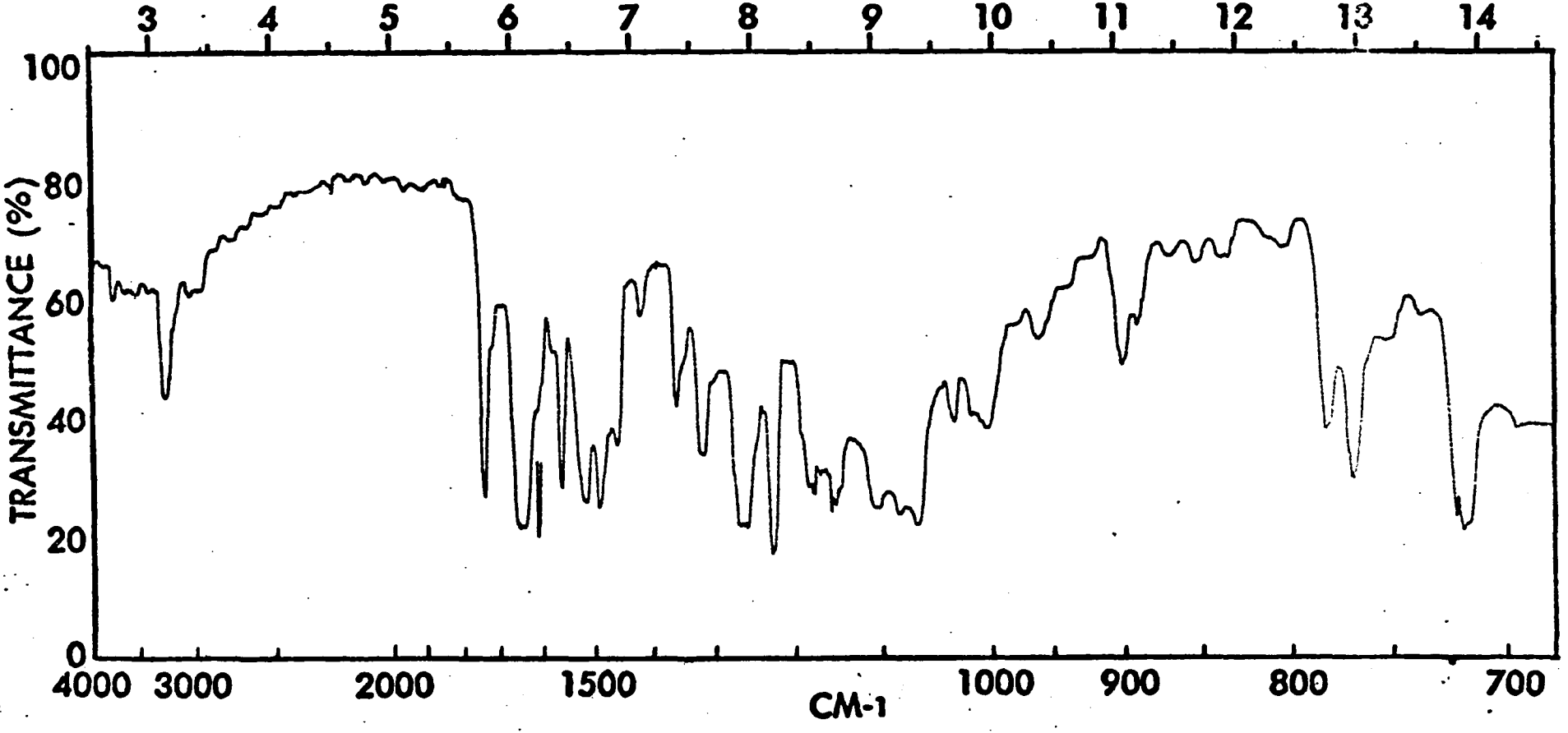
A-34. 3-Benzyl-3,6-dimethyl[4H]-1-oxa-3-azonia-2-boratanaphthalene (88).



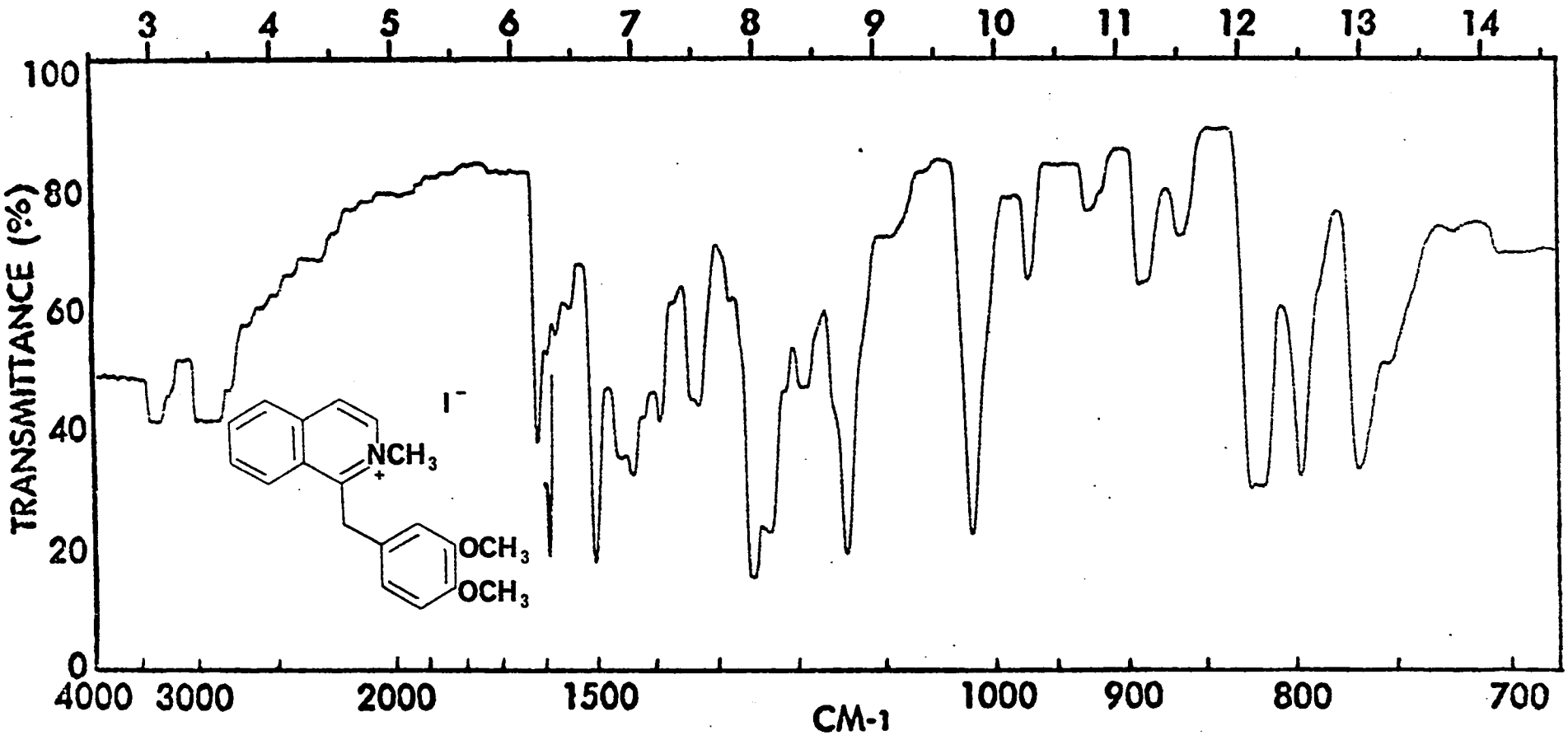
A-35. 2-(Benzyl-p-chlorobenzylaminomethyl)-4-methylphenol (90).



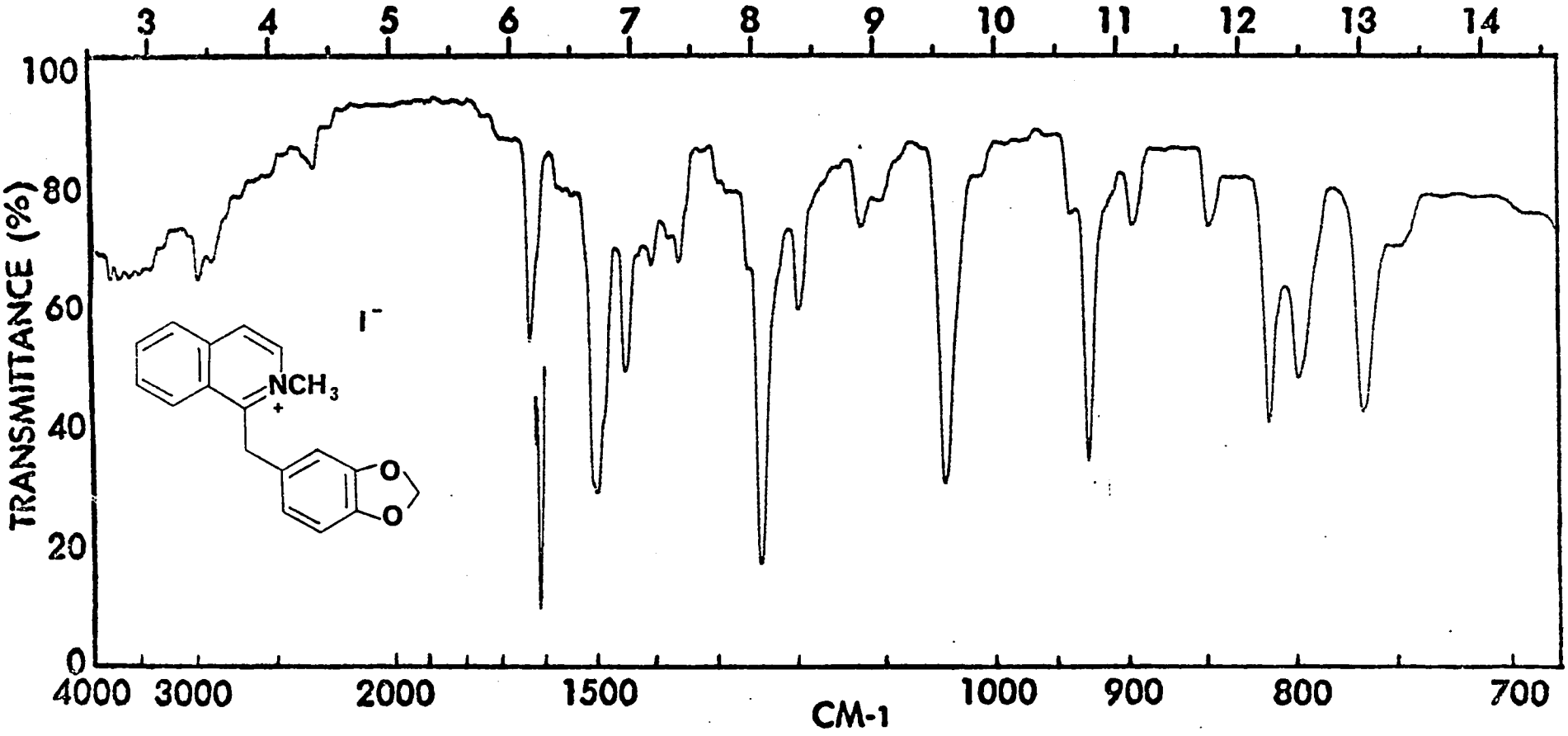
A-36. 2-(Benzylmethylaminomethyl)-4-methoxyphenol (91).



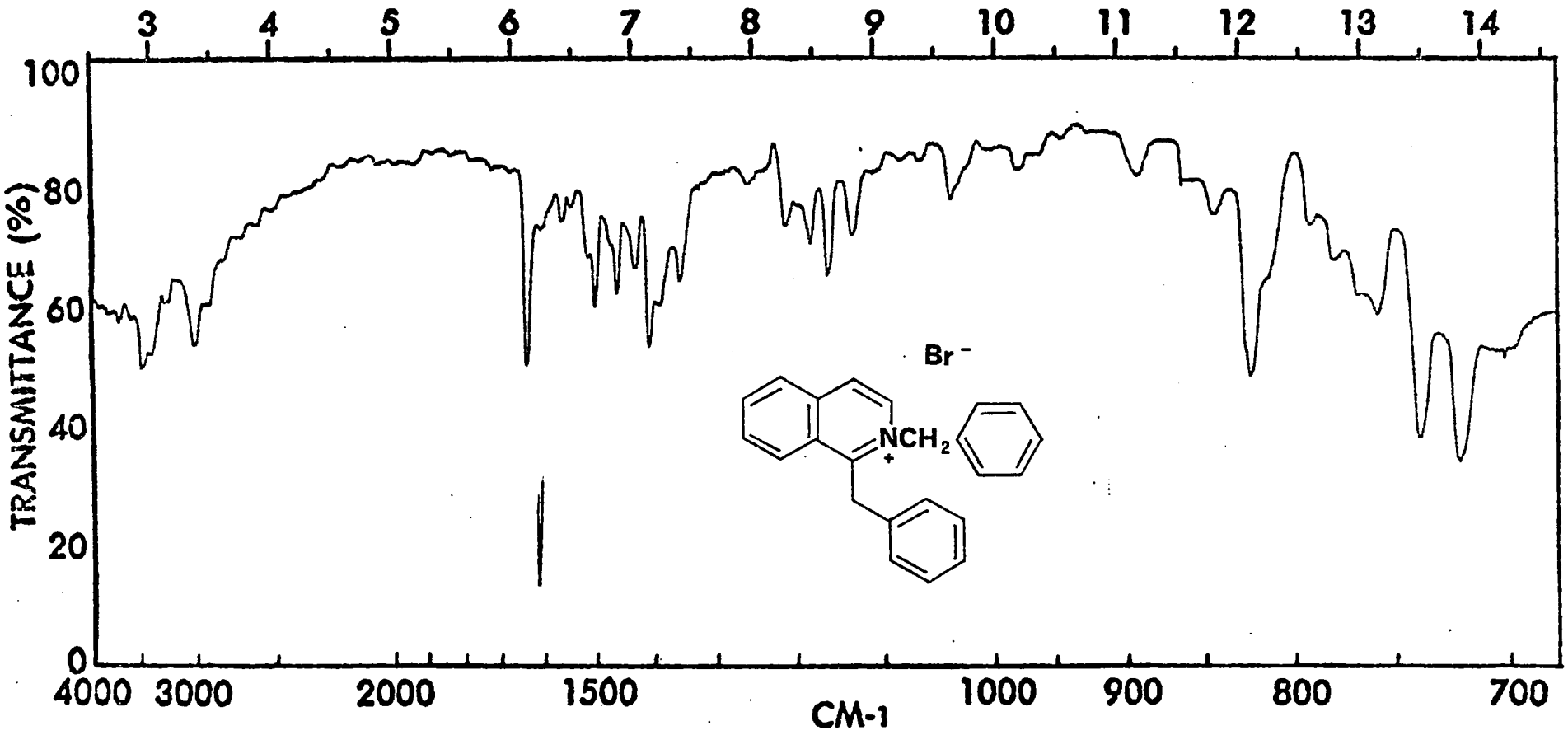
A-37. Compound 105 - Undetermined Structure.



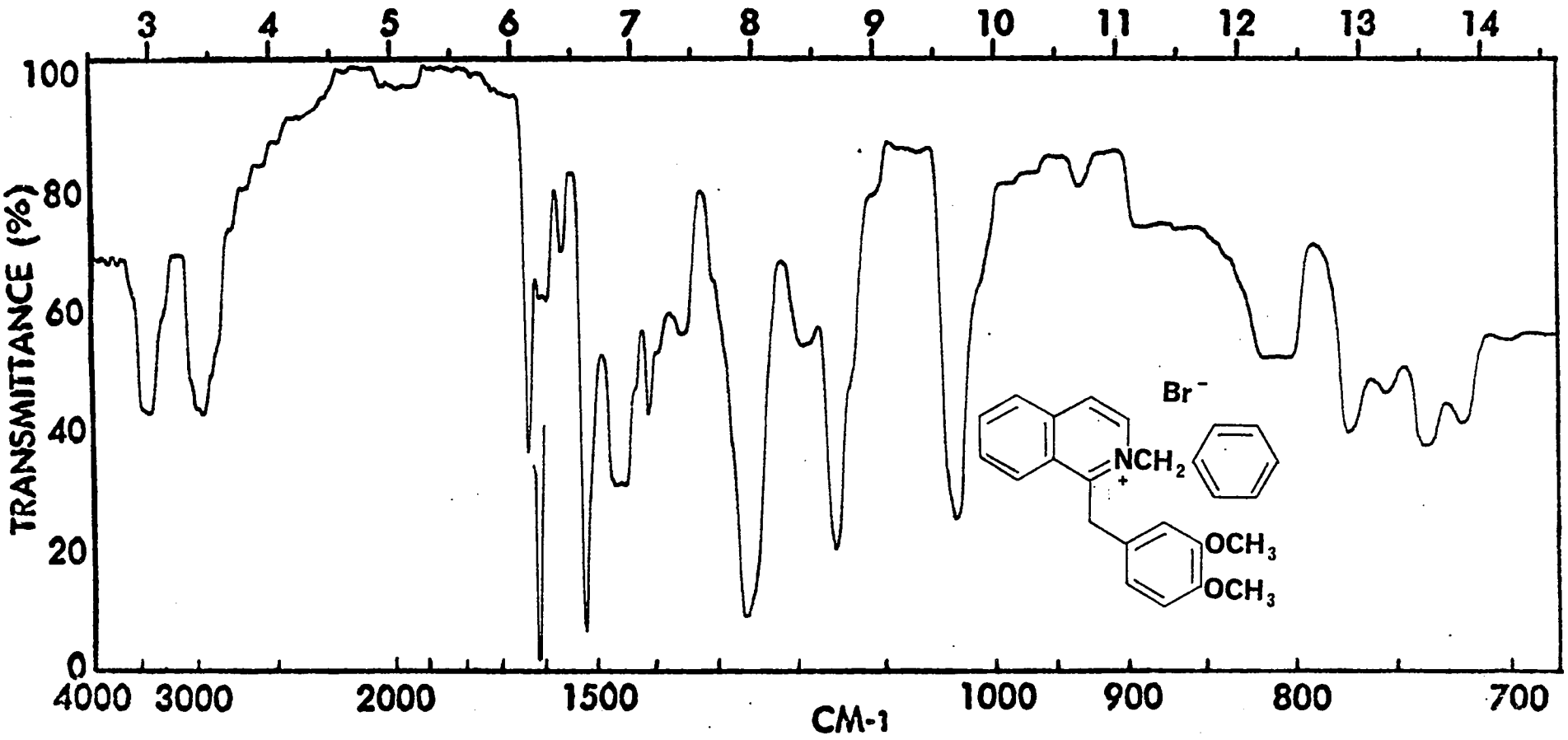
A-38. 1-(3',4'-Dimethoxybenzyl)-2-methylisoquinolinium Iodide (112).



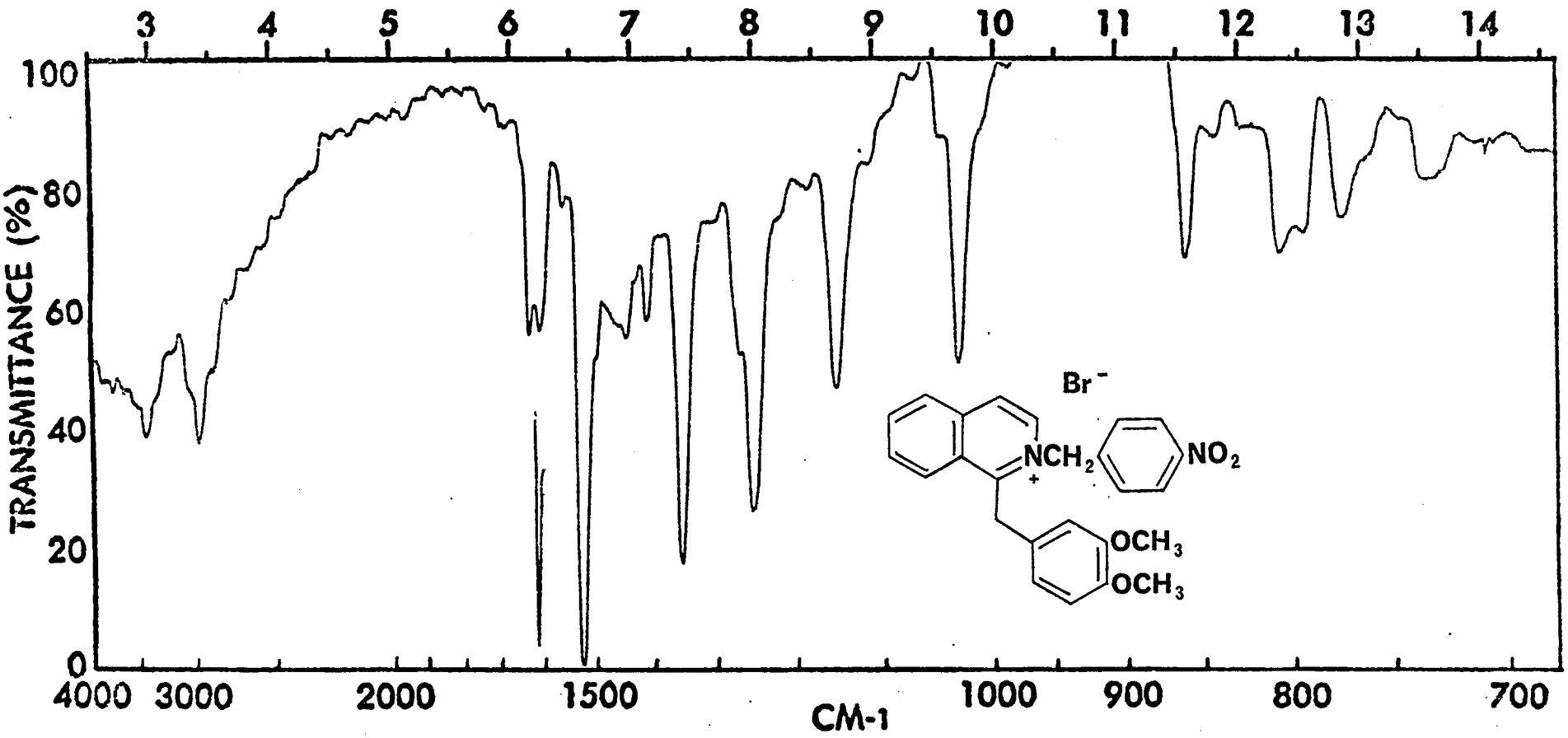
A-39. 1-(3',4'-Methylenedioxybenzyl)-2-methylisoquinolinium Iodide (113).



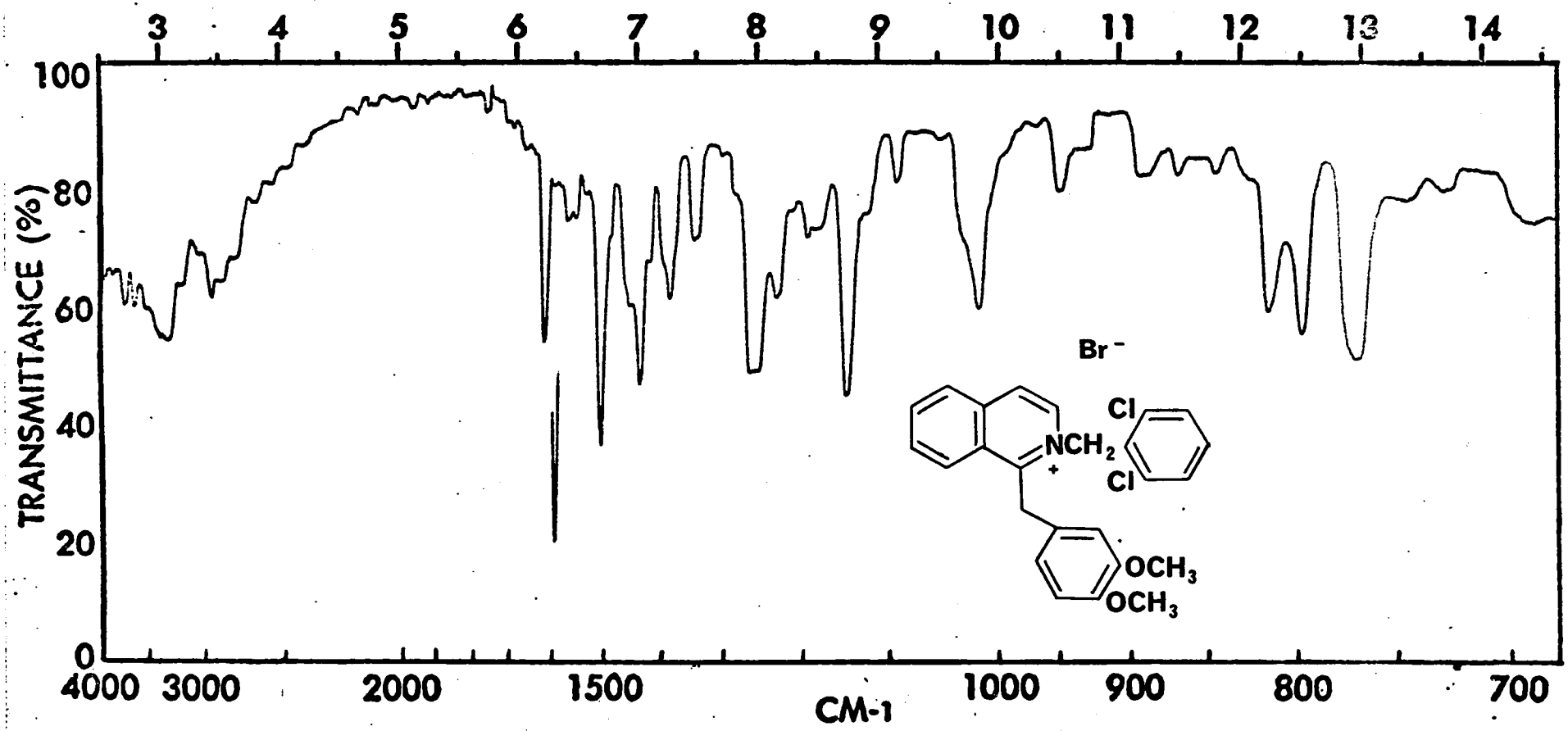
A-40. 1,2-Dibenzylisoquinolinium Bromide (114).



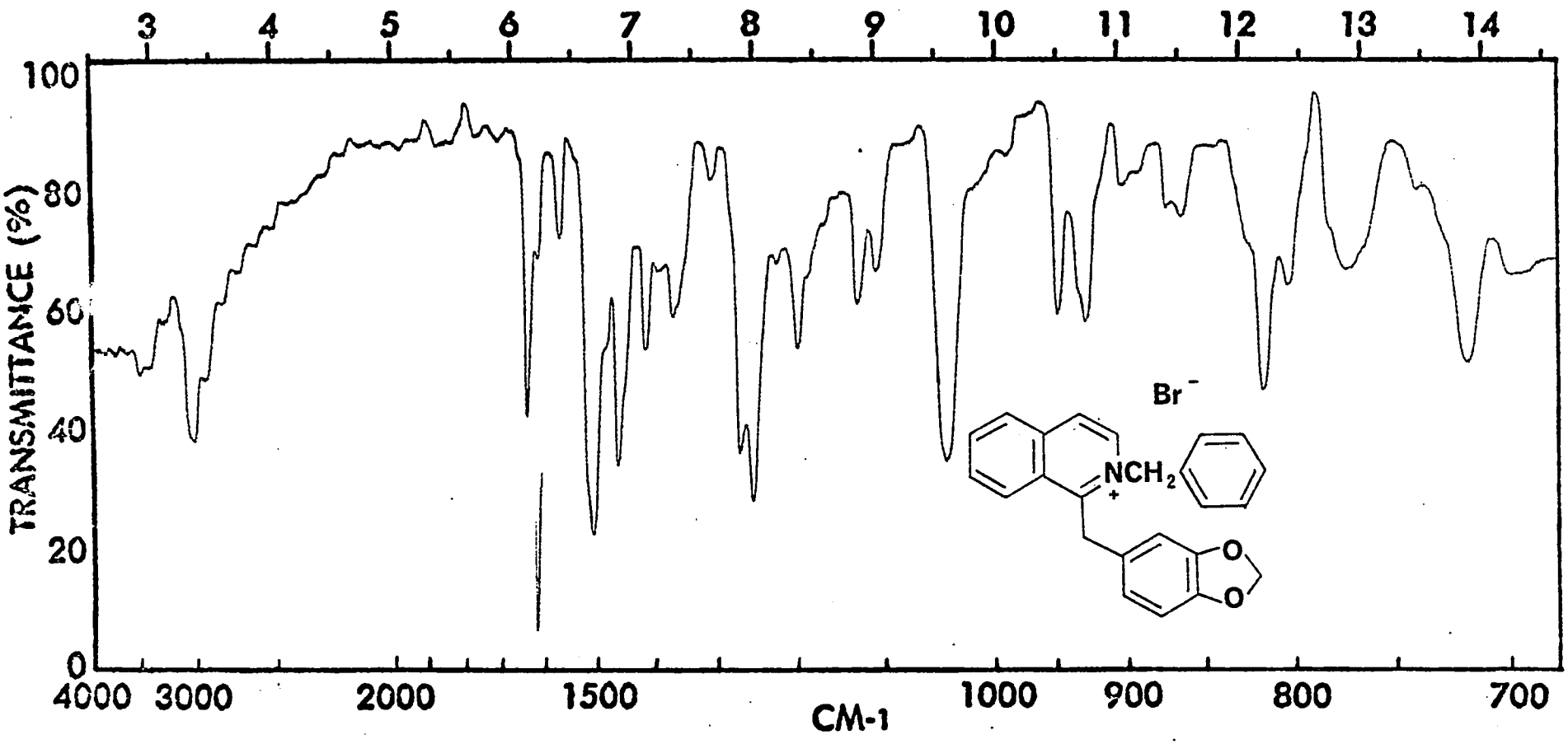
A-41. 1-(3',4'-Dimethoxybenzyl)-2-benzylisoquinolinium Bromide (115).



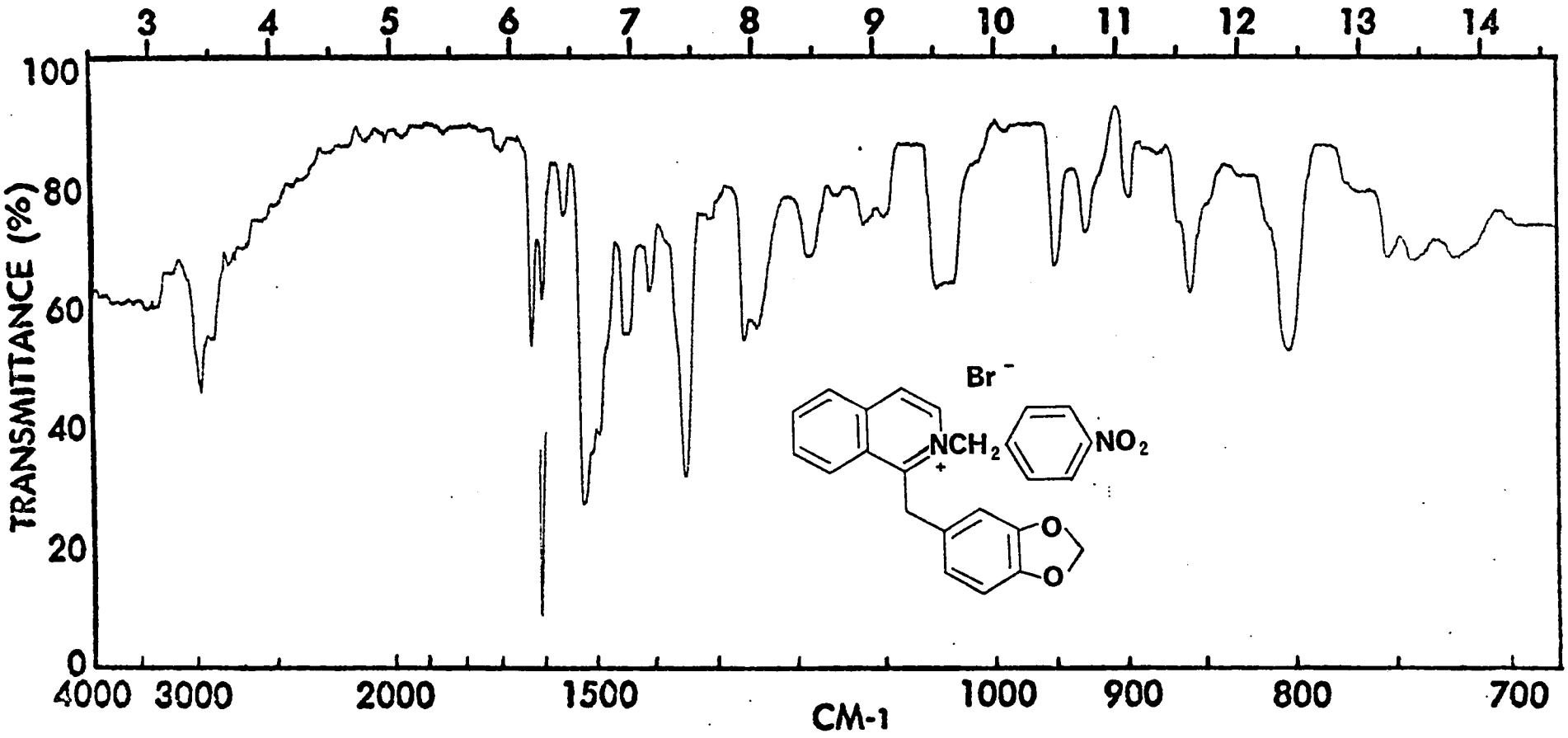
A-42. 1-(3',4'-Dimethoxybenzyl)-2-(4"-nitrobenzyl)isoquinolinium Bromide (116).



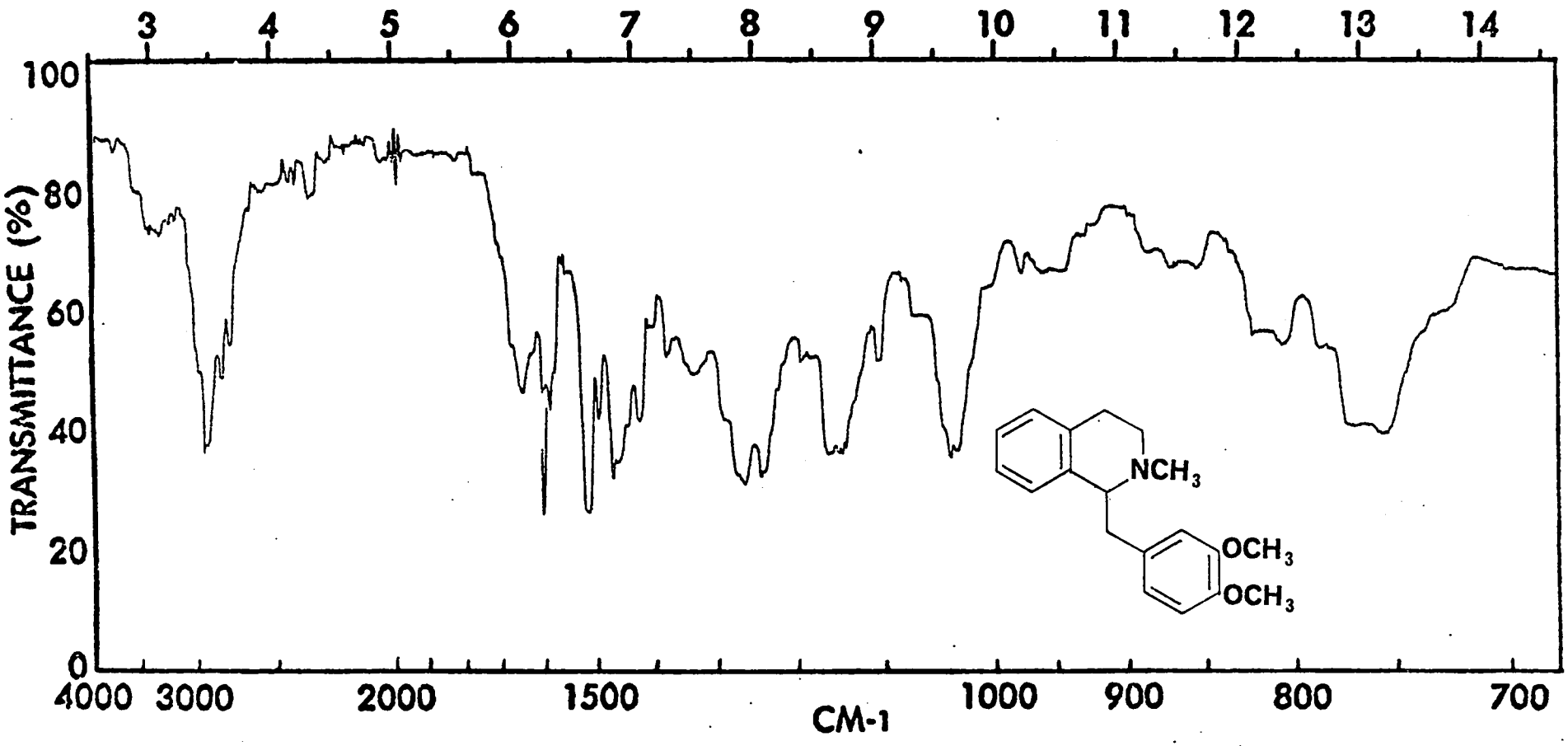
A-43. 1-(3',4'-Dimethoxybenzyl)-2-(2",6"-dichlorobenzyl)isoquinolinium Bromide (117).



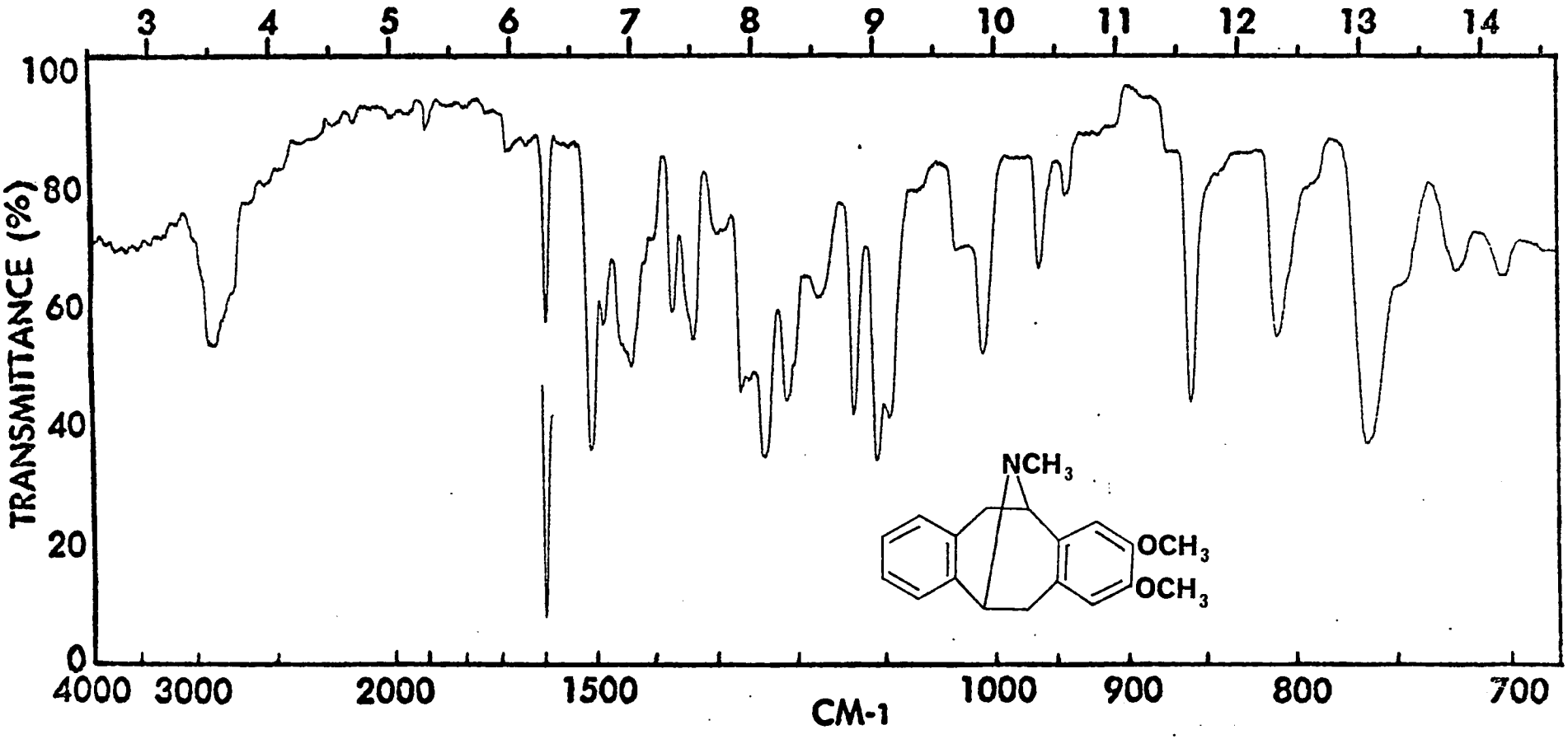
A-44. 1-(3',4'-Methylenedioxybenzyl)-2-benzylisoquinolinium Bromide (118).



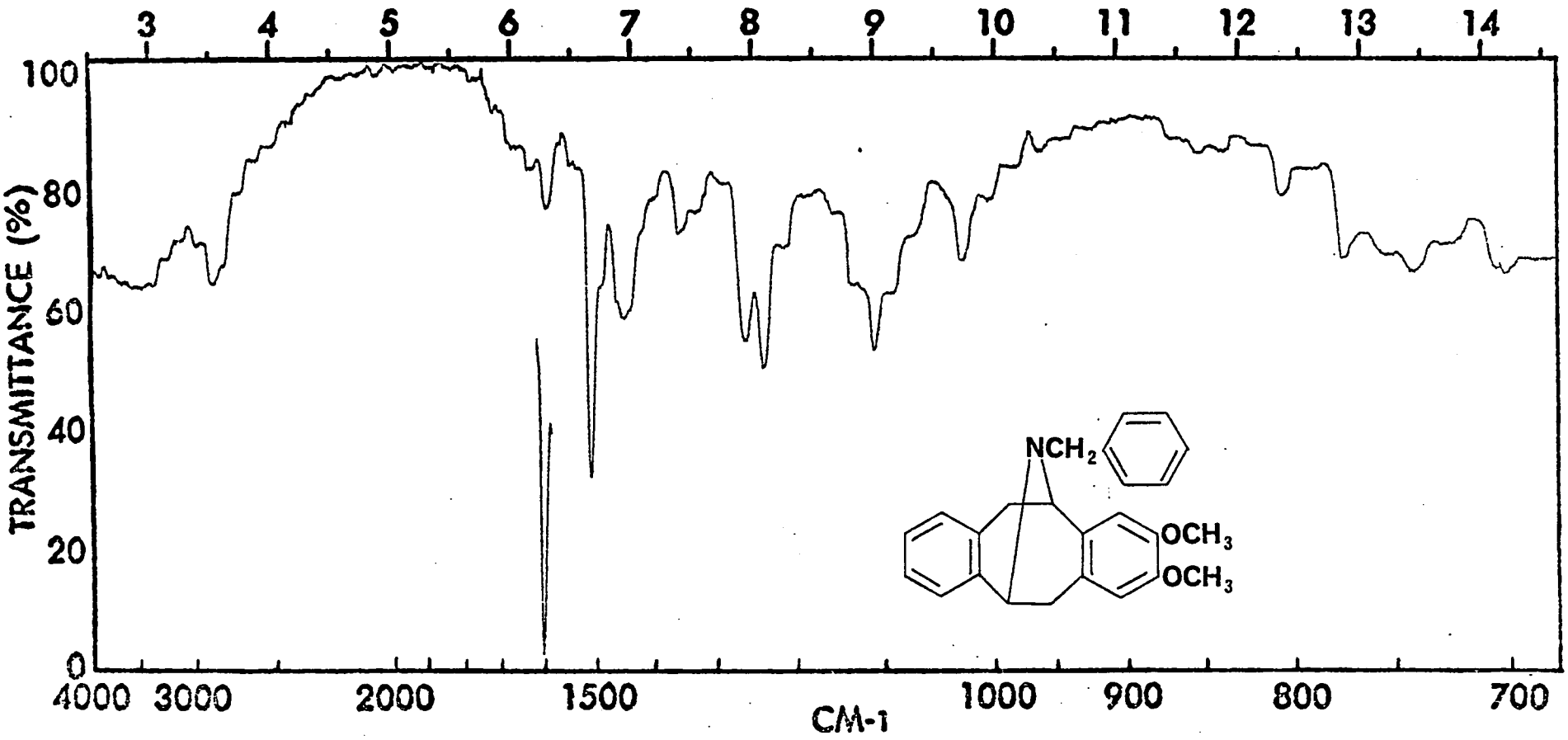
A-45. 1-(3',4'-Methylenedioxybenzyl)-2-(4"-nitrobenzyl)isoquinolinium Bromide (119).



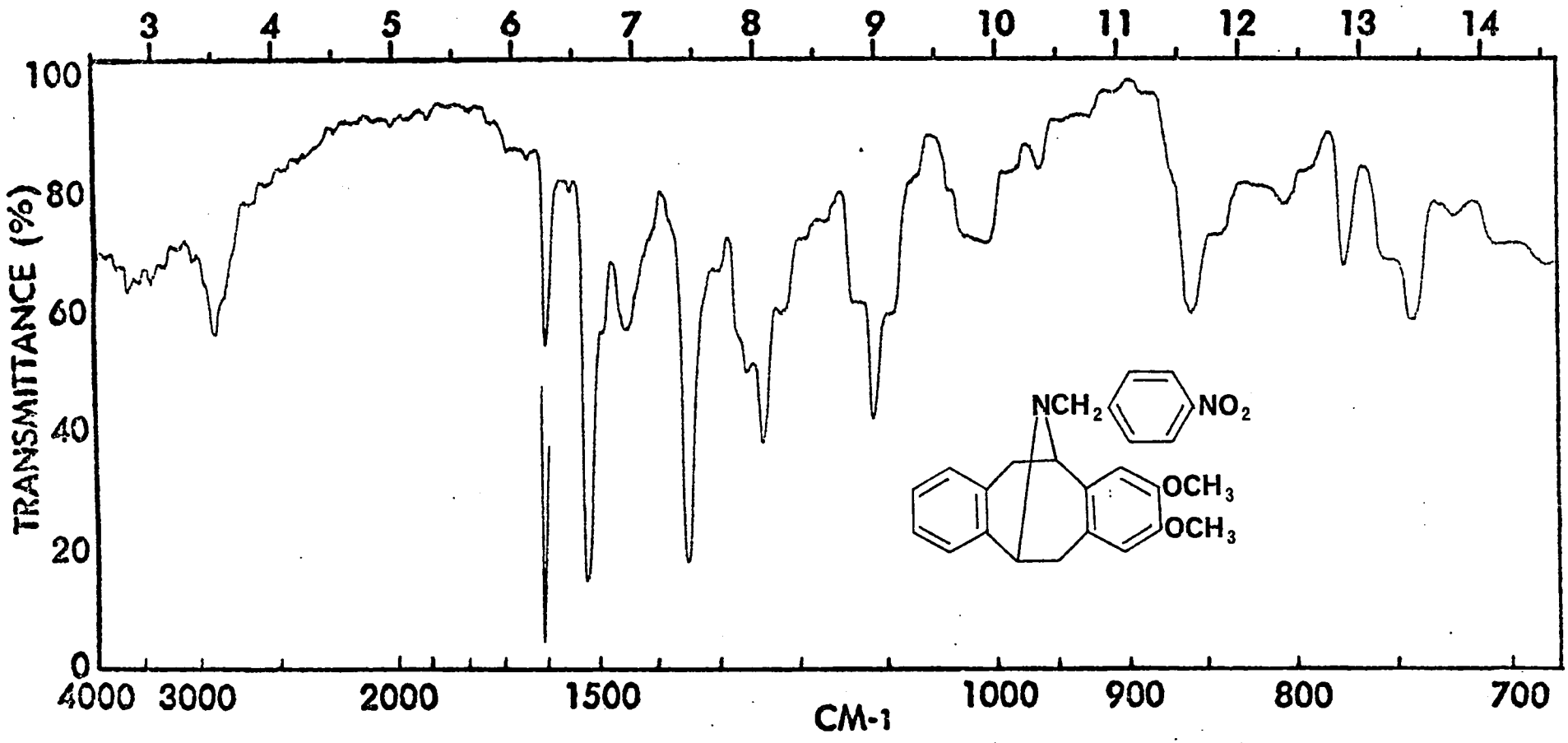
A-46. 1-(3',4'-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (120).



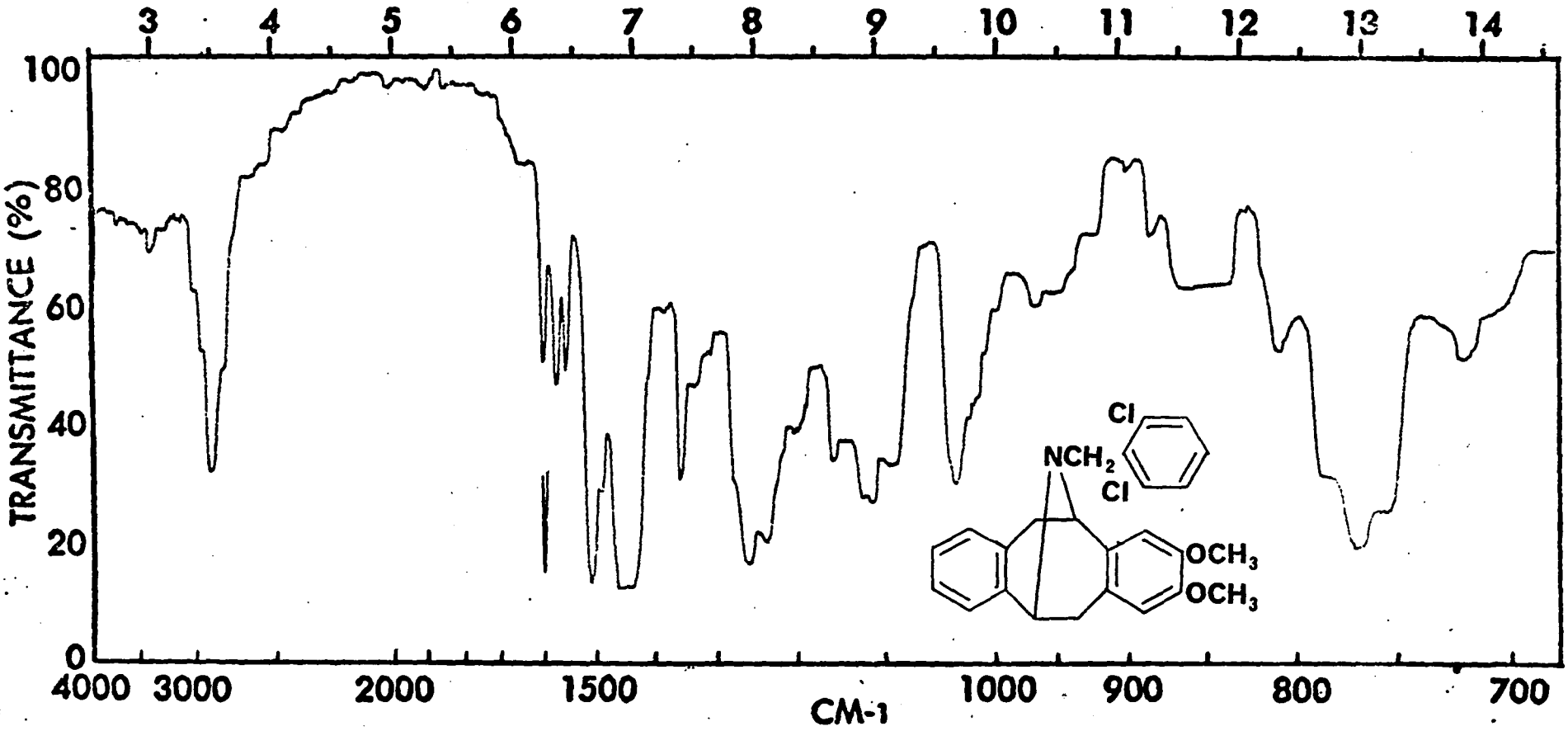
A-47. 2,3-Dimethoxy-N-methylpavinane (128).



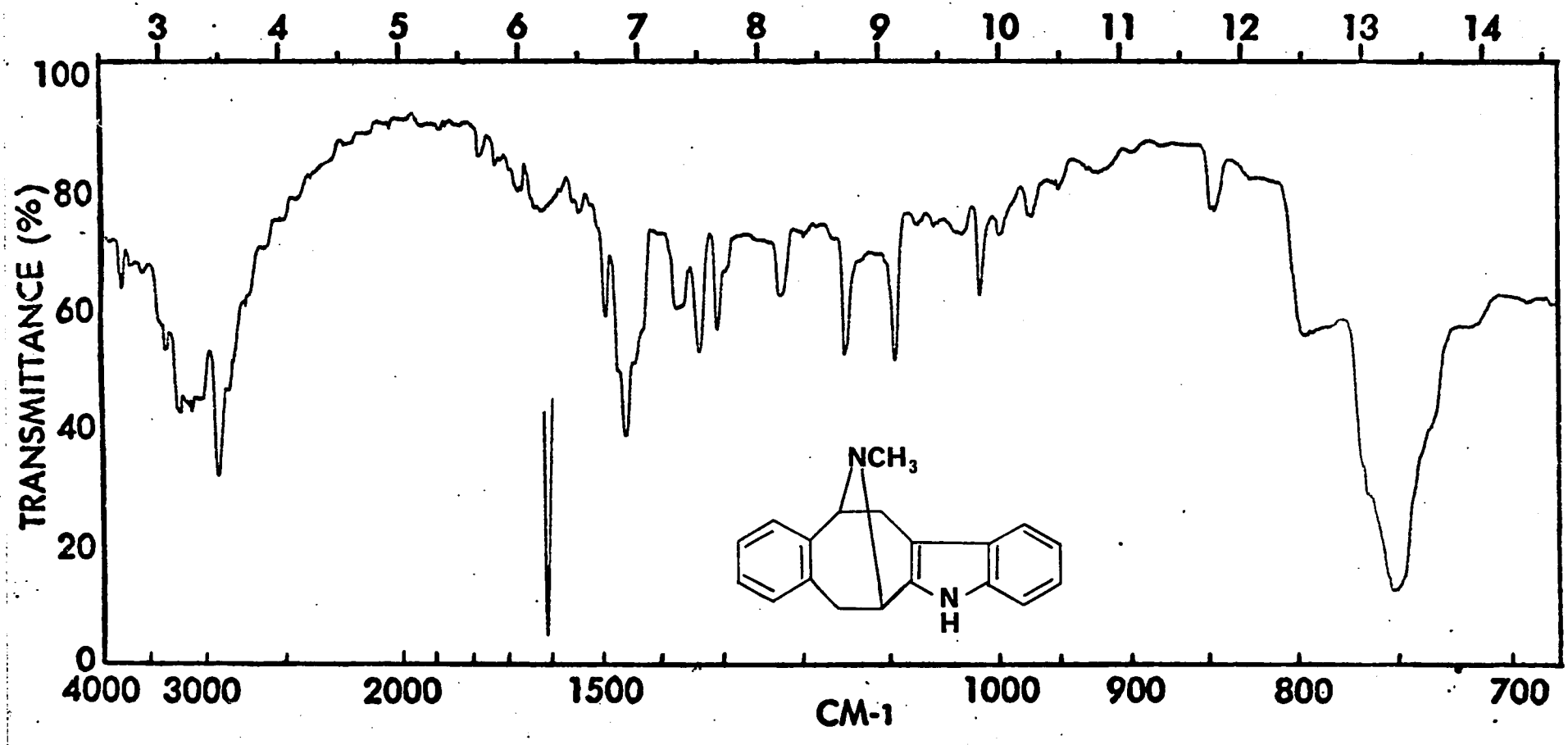
A-48. 2,3-Dimethoxy-N-benzylpavinane (129).



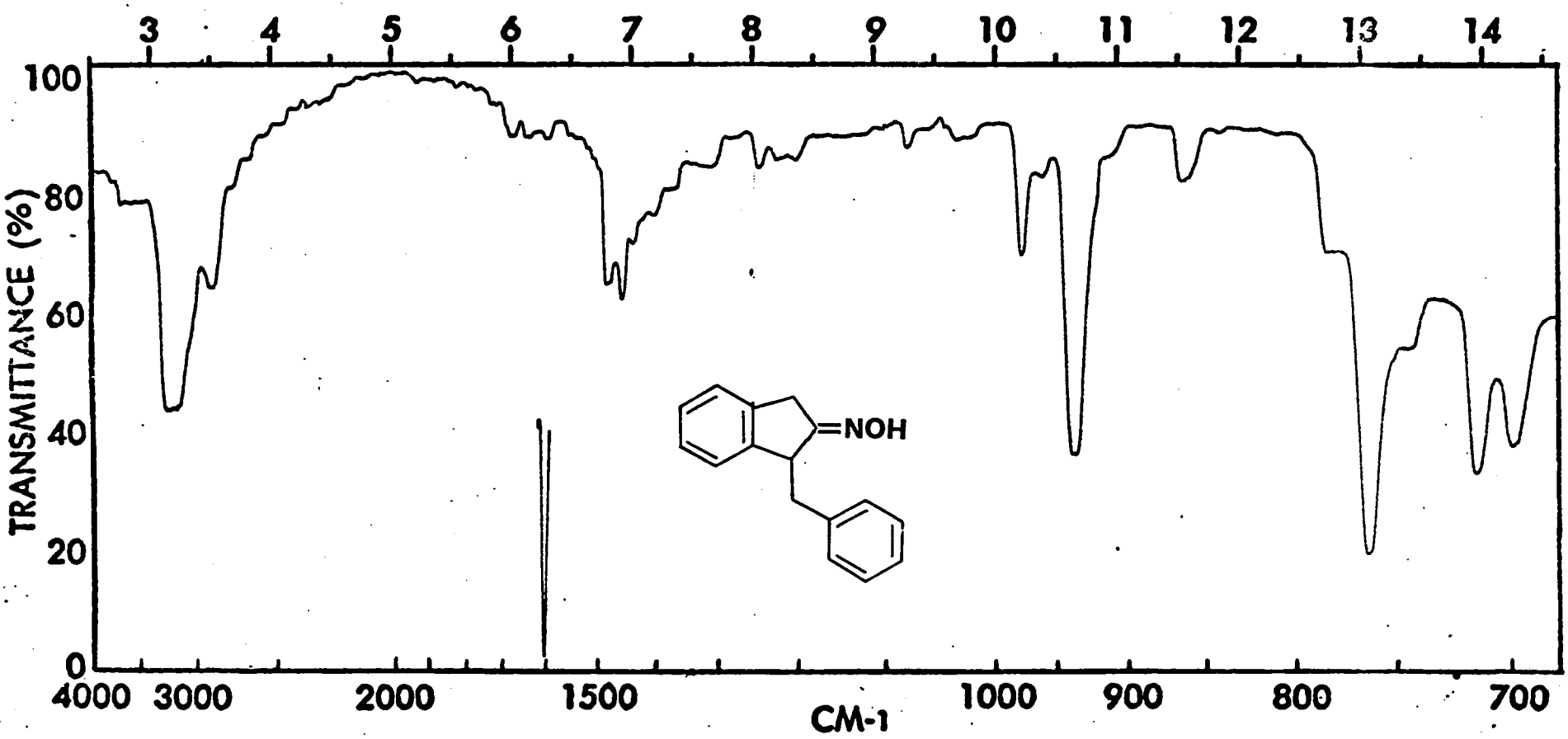
A-49. 2,3-Dimethoxy-N-(4'-nitrobenzyl)pavinane (130).



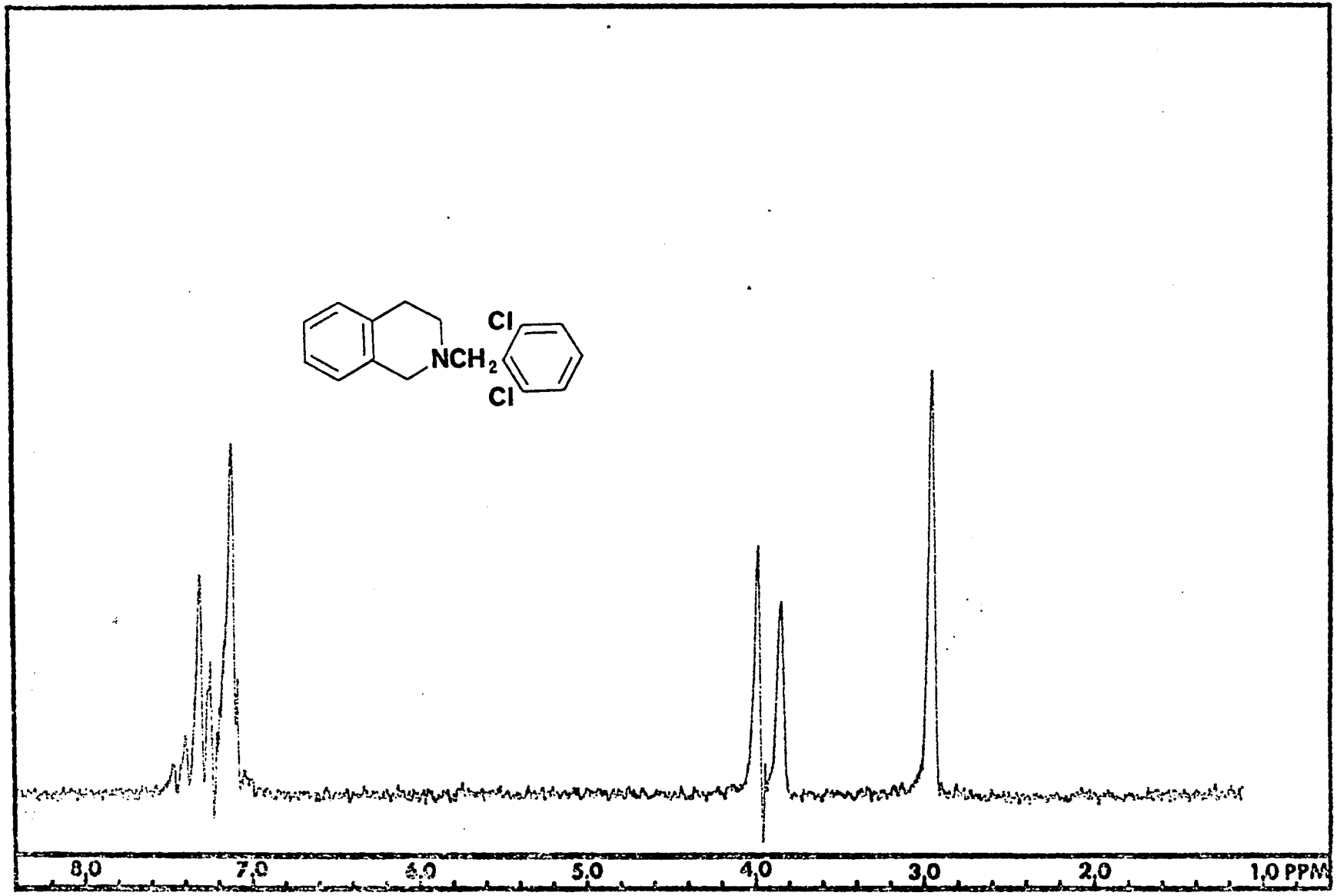
A-50. 2,3-Dimethoxy-N-(2',6'-dichlorobenzyl)pavinane (131).



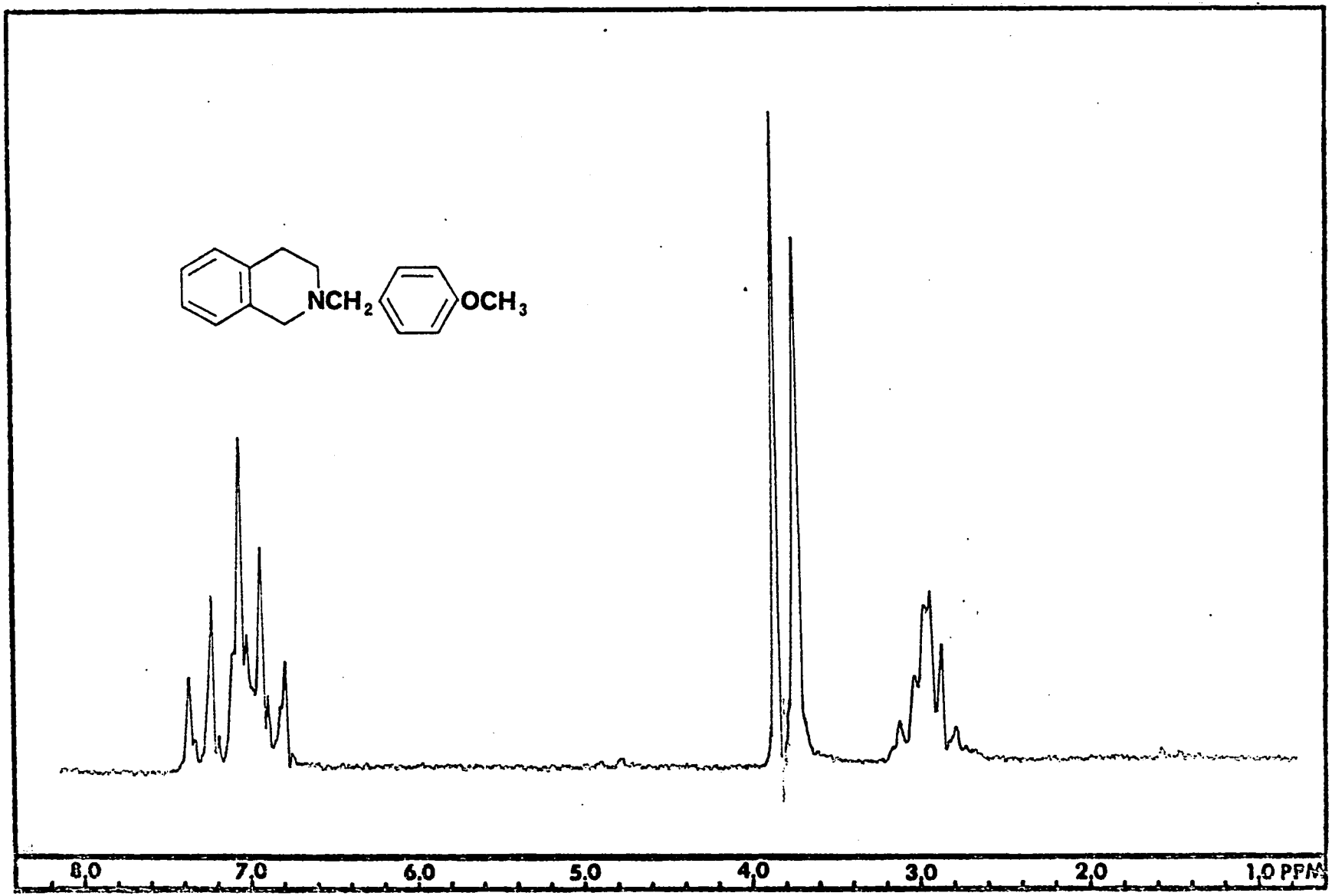
A-51. 14-Methyl-6,7,12,13-tetrahydro-6,12-imino-5H-benzo[5,6]cyclooct[1,2-b]indole (152).



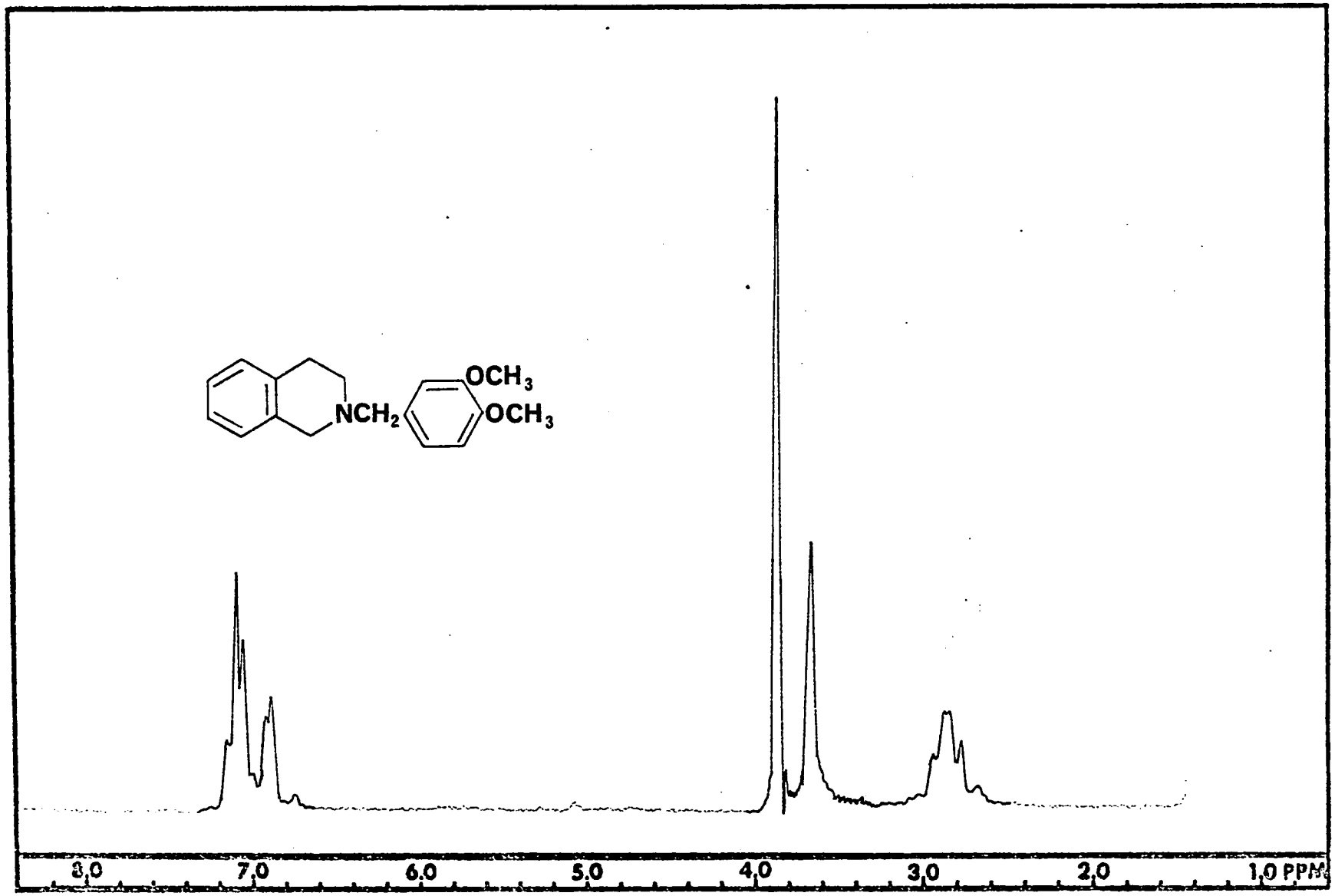
A-52. 1-Benzyl-2-indanonoxime (146).



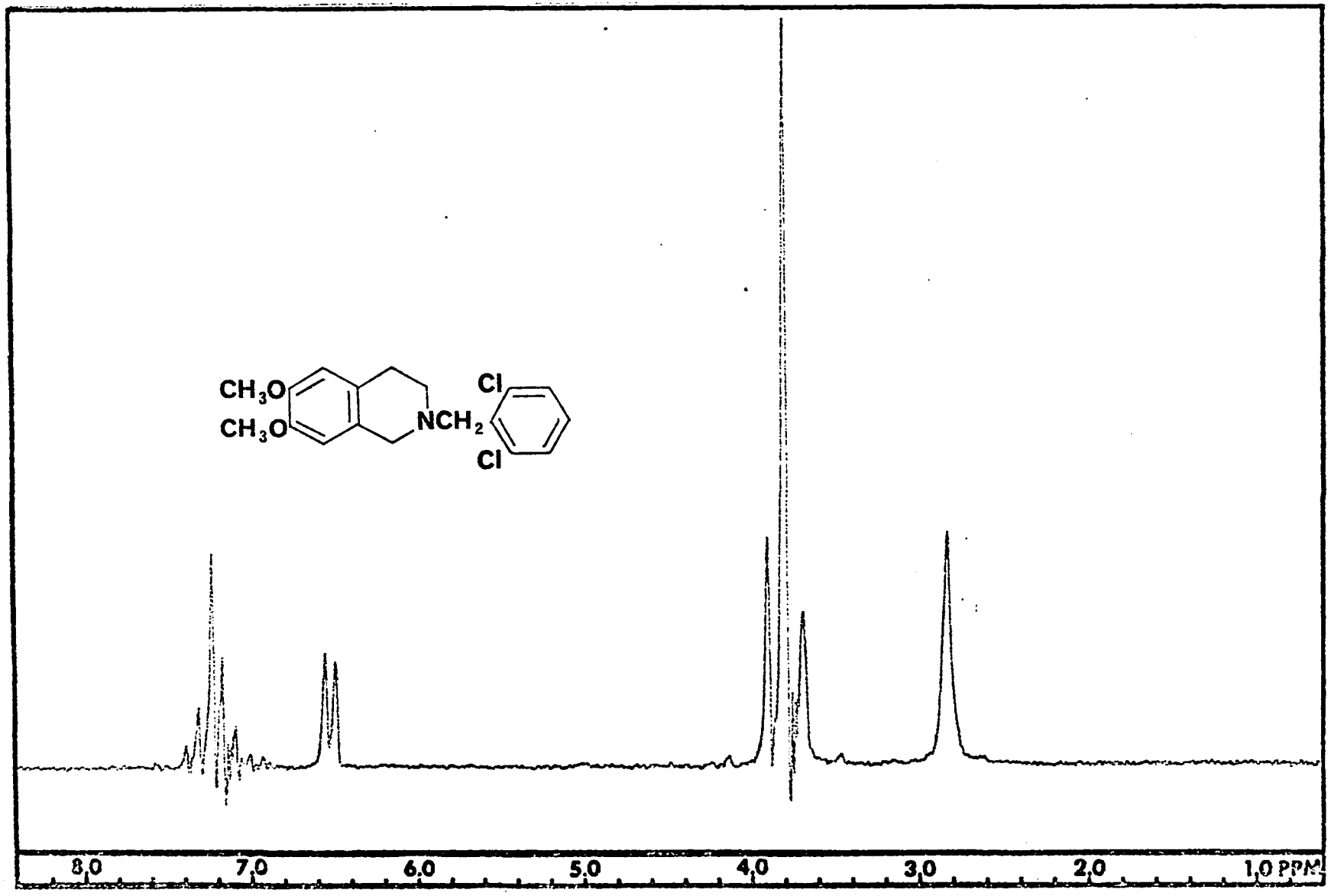
B-1. 2-(2',6'-Dichlorobenzyl)-1,2,3,4-tetrahydroisoquinoline (40).



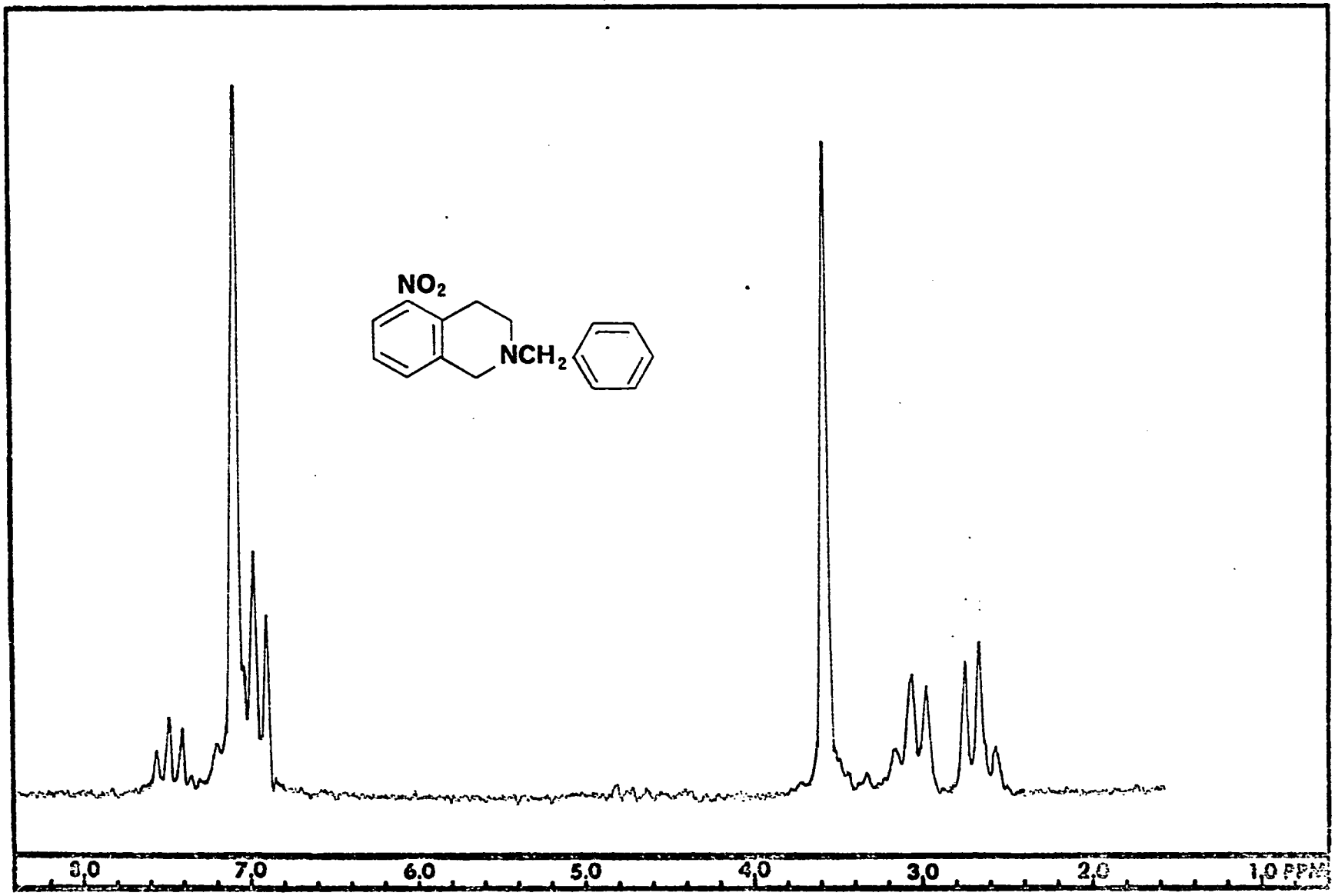
B-2. 2-(4'-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (43).



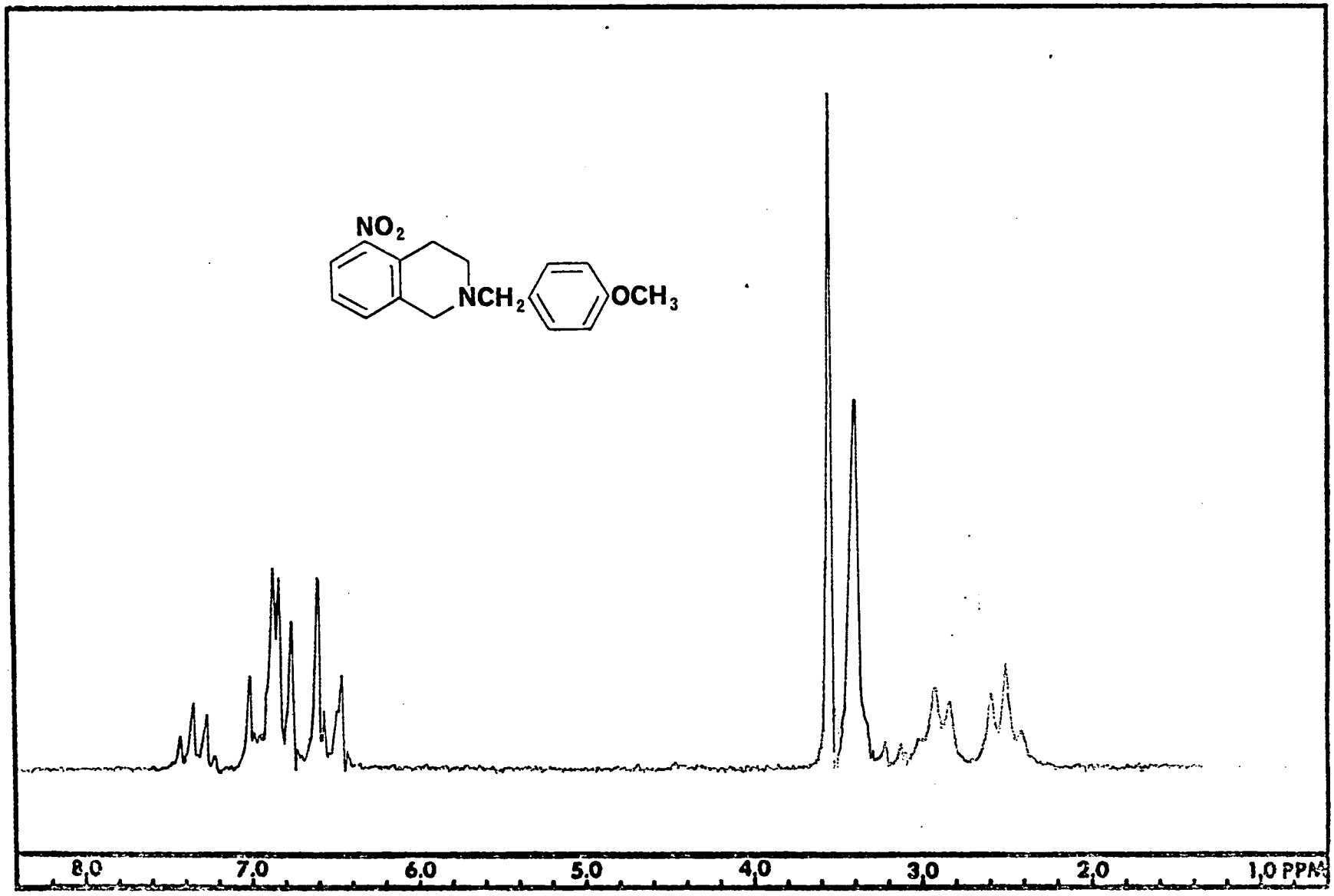
B-3. 2-(3',4'-Dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (<u>44</u>).



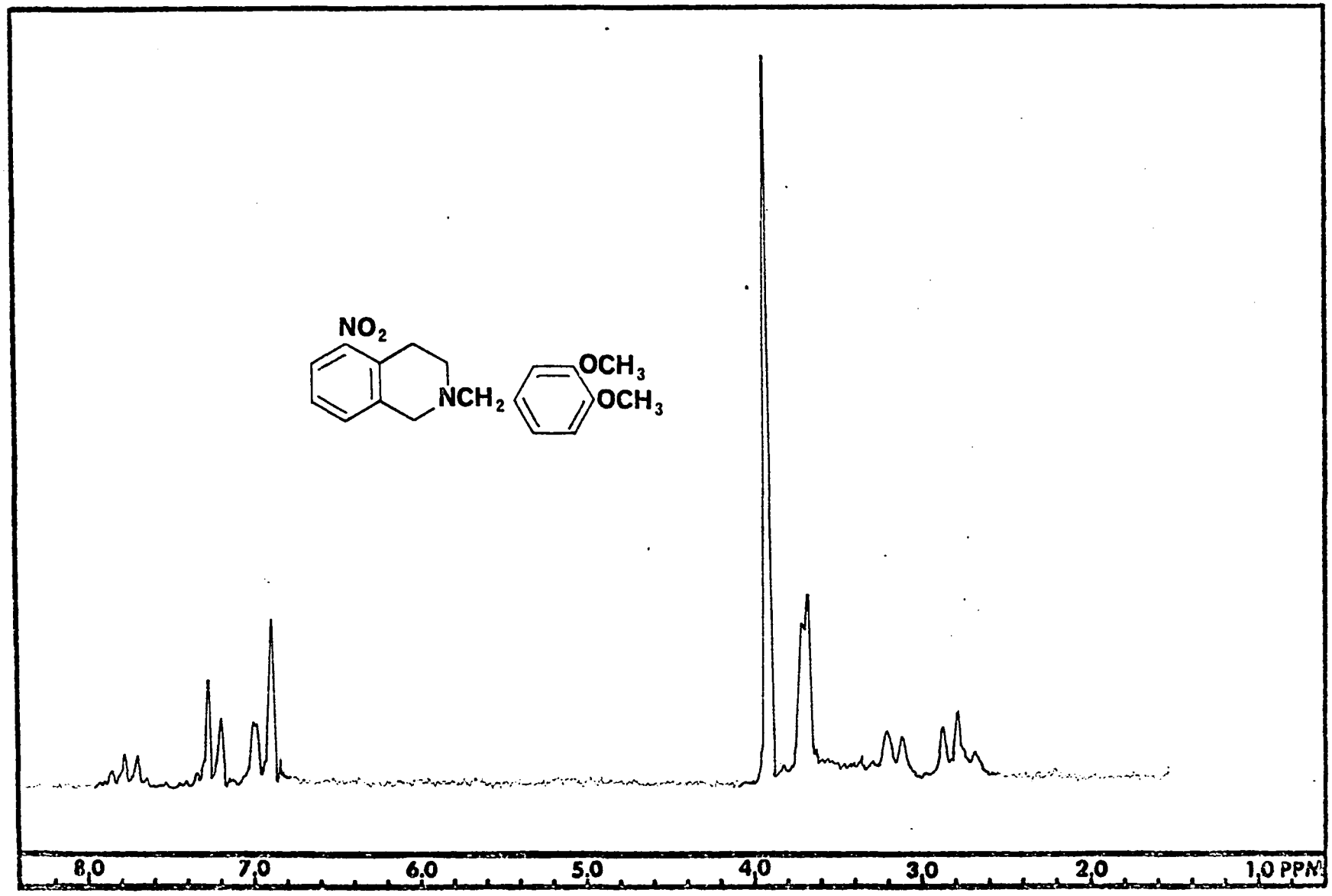
B-4. 2-(2',6'-Dichlorobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (49).



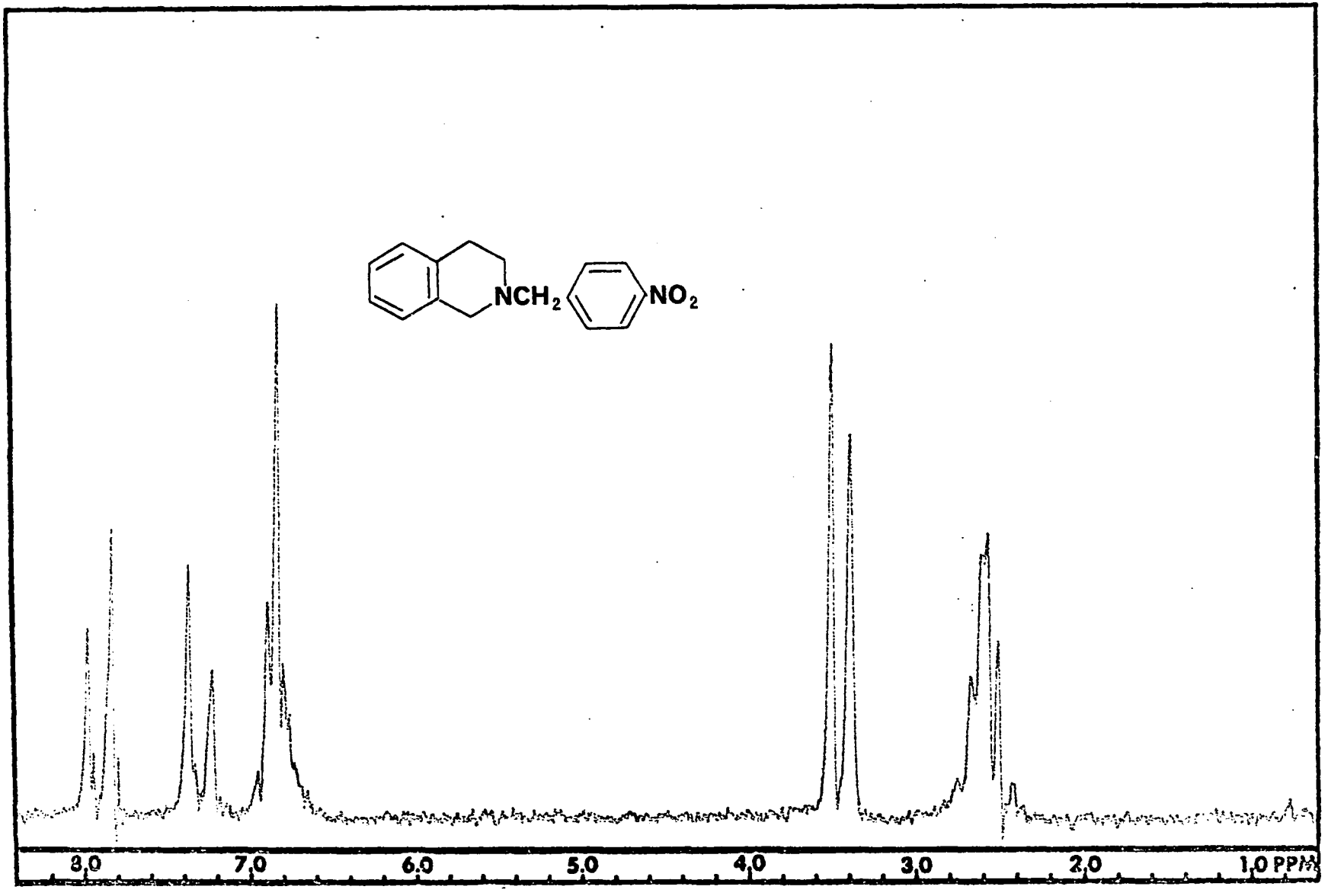
B-5. 2-Benzyl-5-nitro-1,2,3,4-tetrahydroisoquinoline (54)



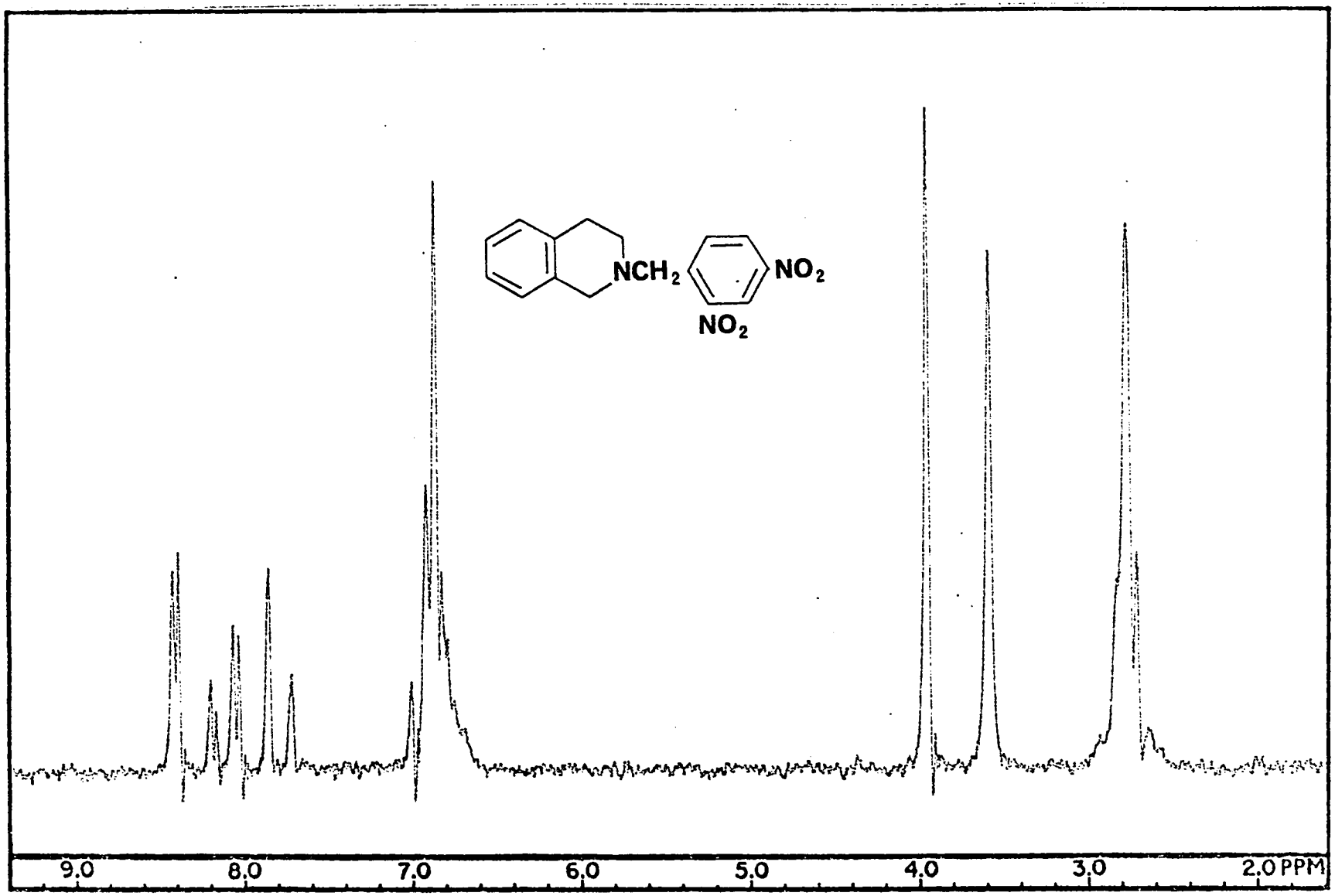
B-6. 2-(4'-Methoxybenzyl)-5-nitro-1,2,3,4-tetrahydroisoquinoline (55).



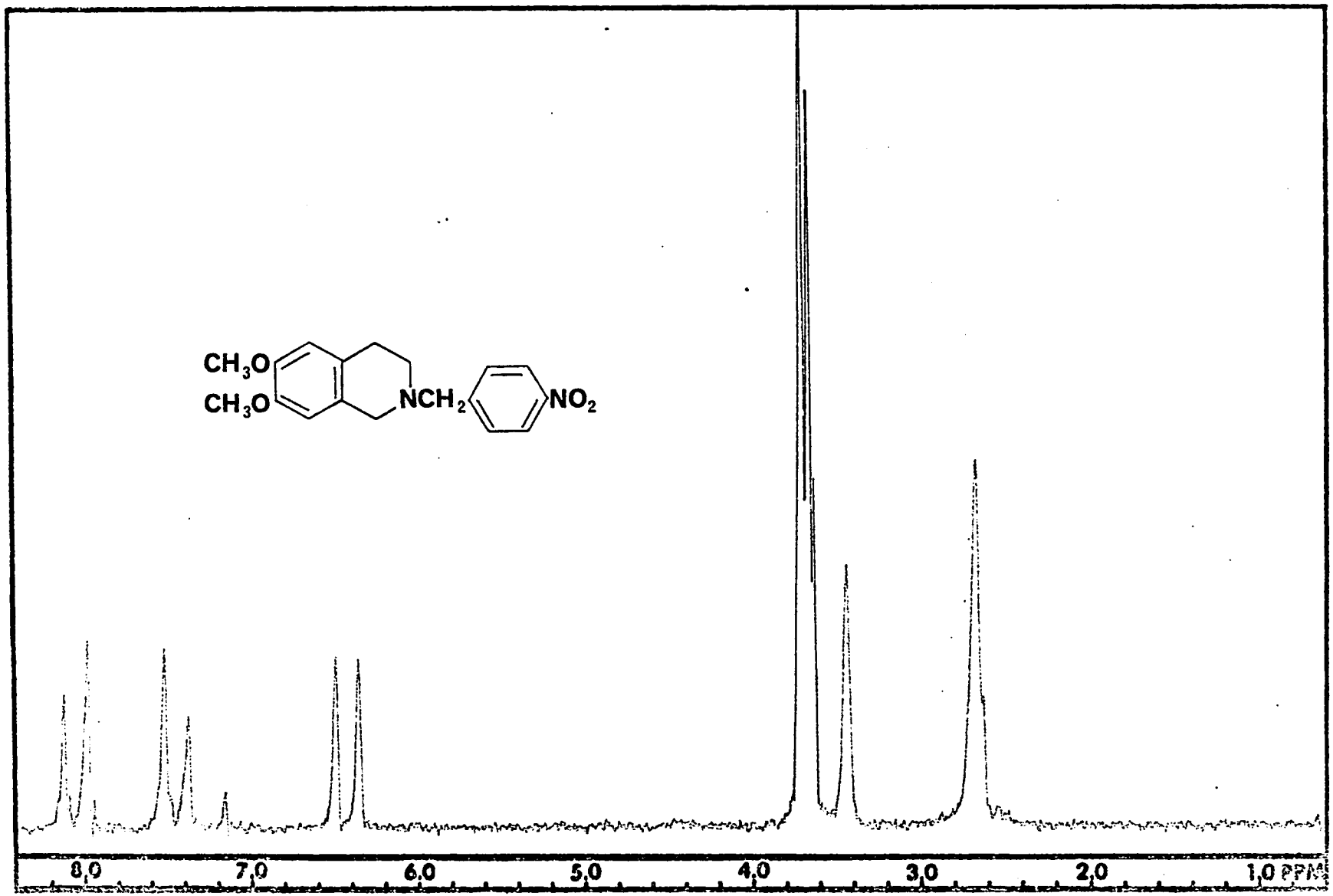
B-7. 2-(3',4'-Dimethoxybenzyl)-5-nitro-1,2,3,4-tetrahydroisoquinoline (56).



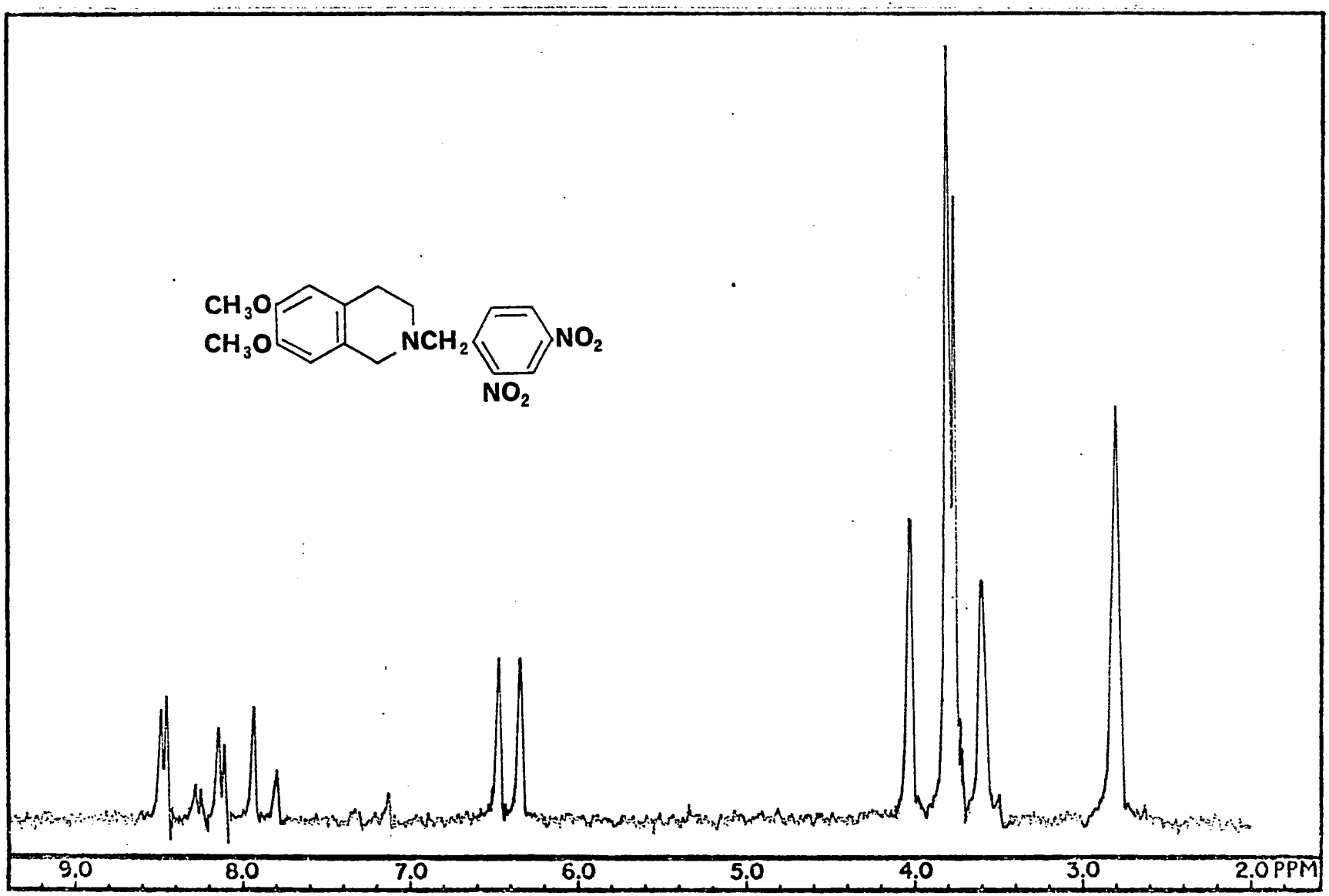
B-8. 2-(4'-Nitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (41).



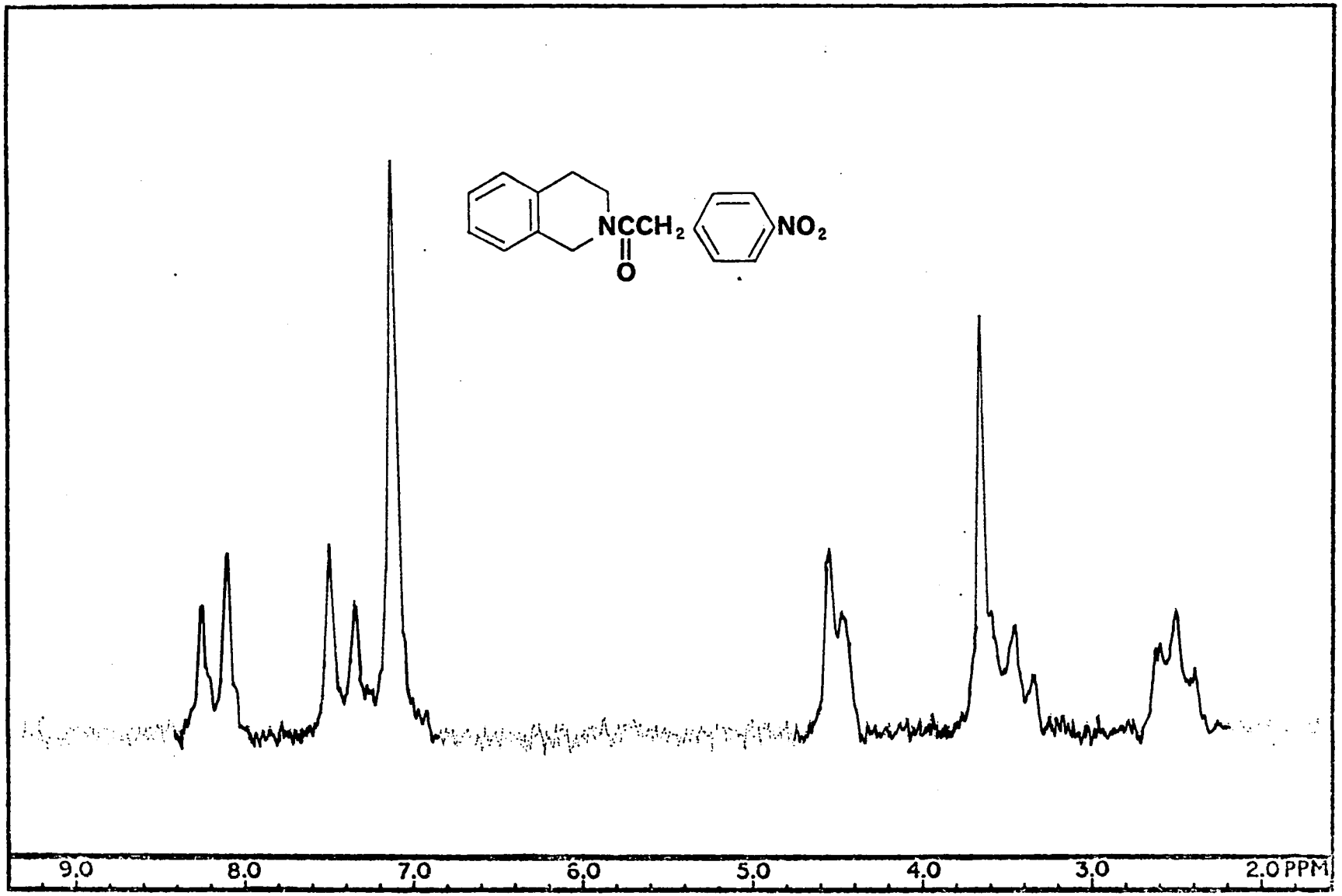
B-9. 2-(2',4'-Dinitrobenzyl)-1,2,3,4-tetrahydroisoquinoline (42).



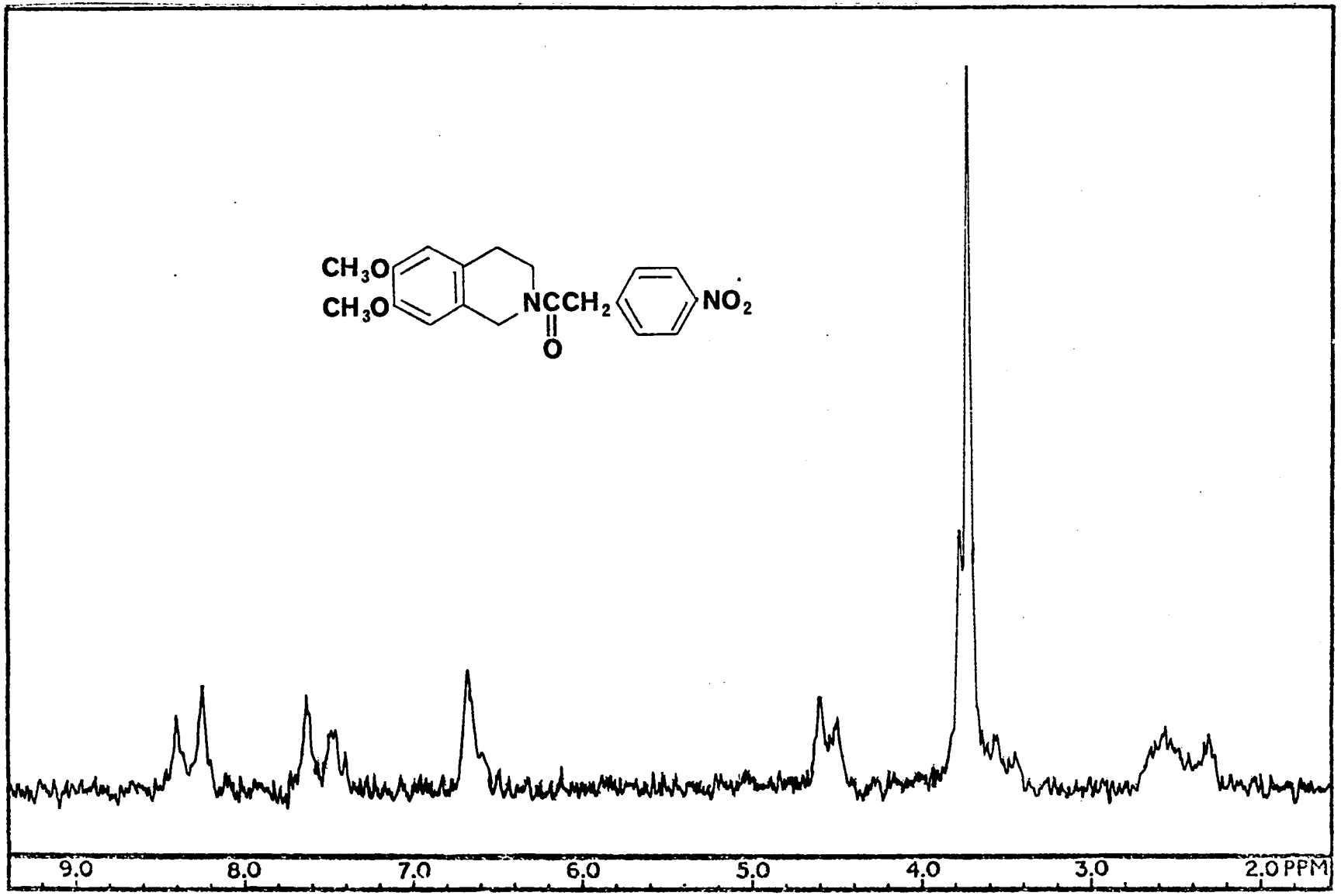
B-10. 2-(4'-Nitrobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (50).



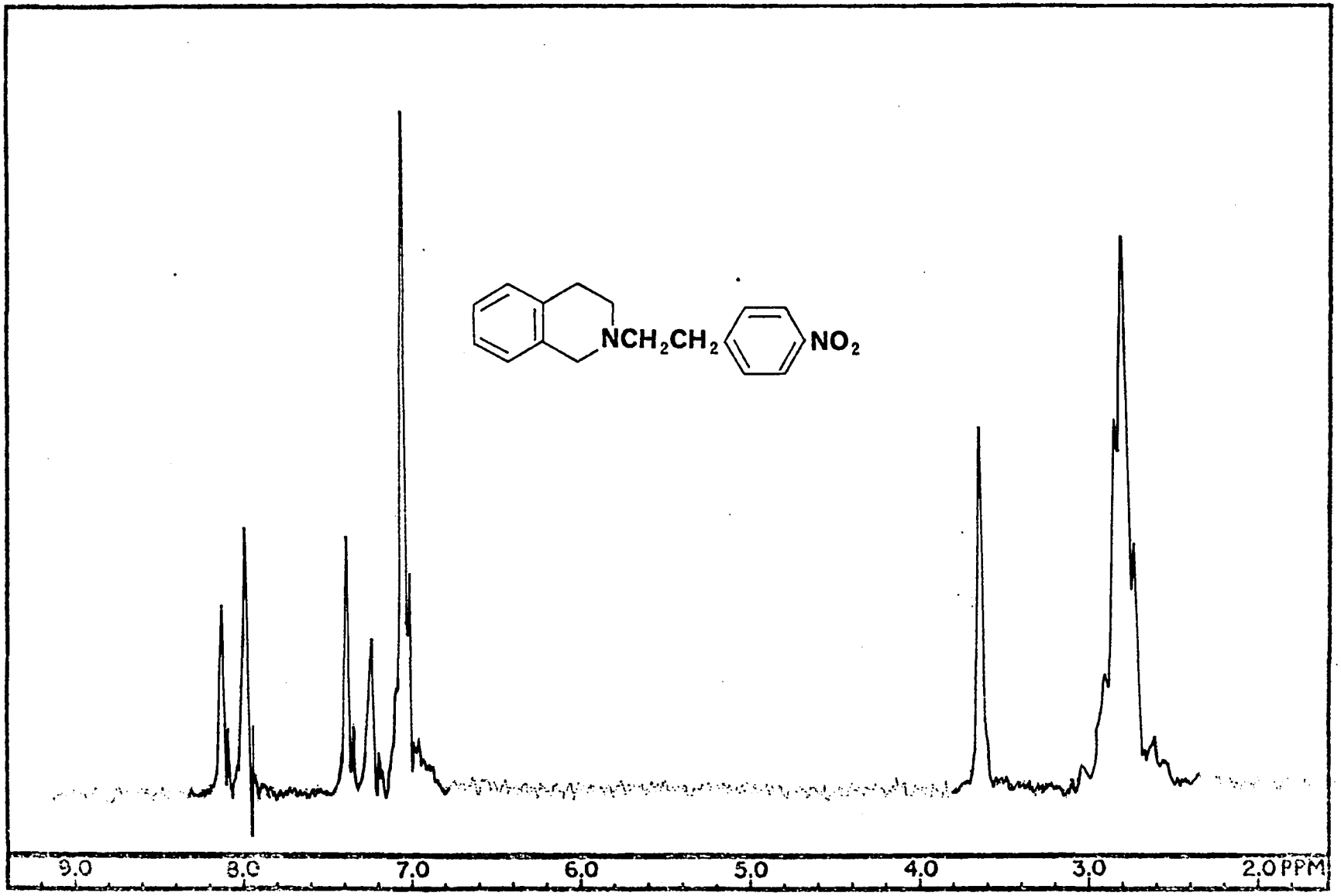
B-11. 2-(2',4'-Dinitrobenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (51).



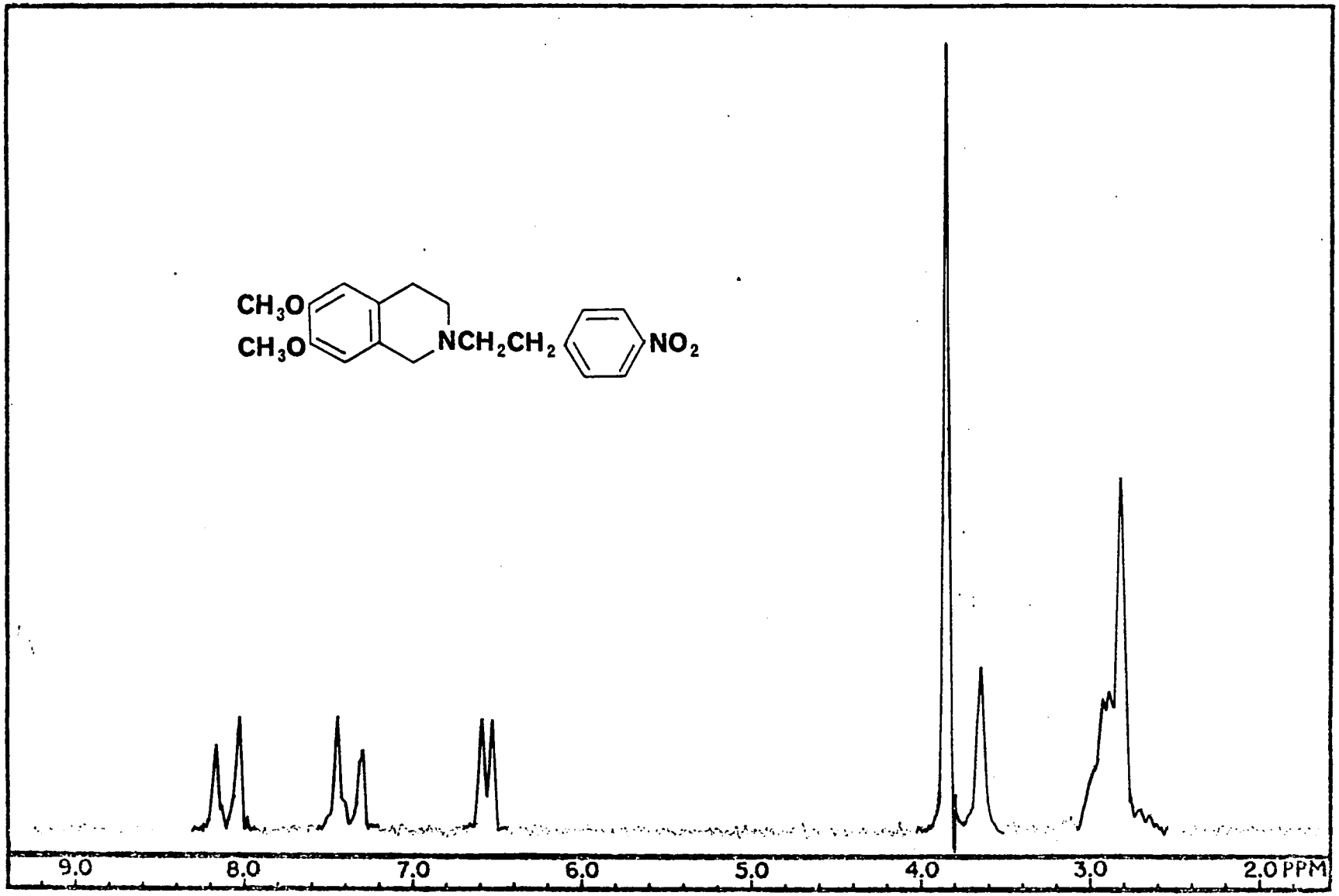
B-12. 2-(4'-Nitrophenacetyl)-1,2,3,4-tetrahydroisoquinoline (59).



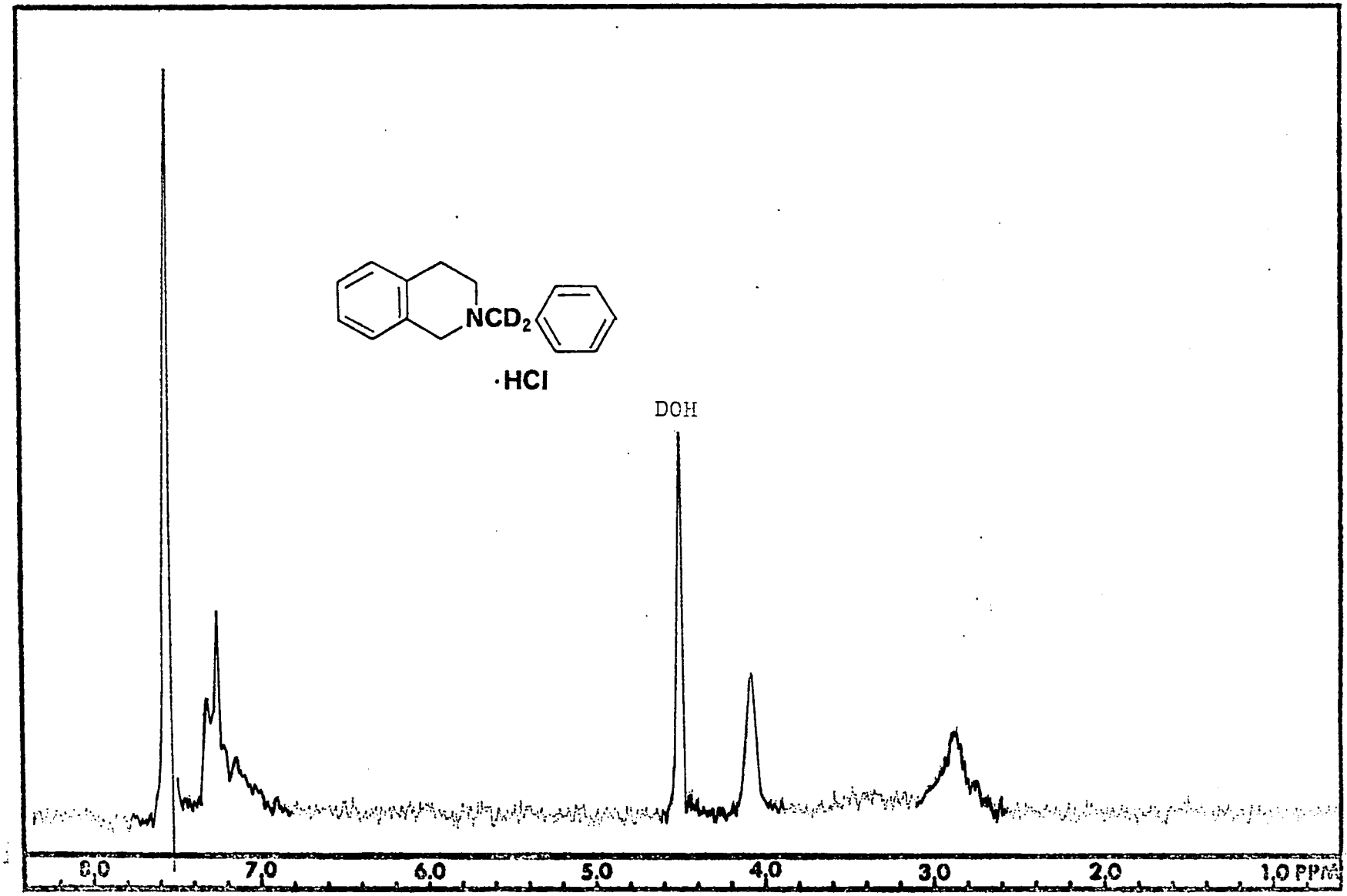
B-13. 2-(4'-Nitrophenacetyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (60).



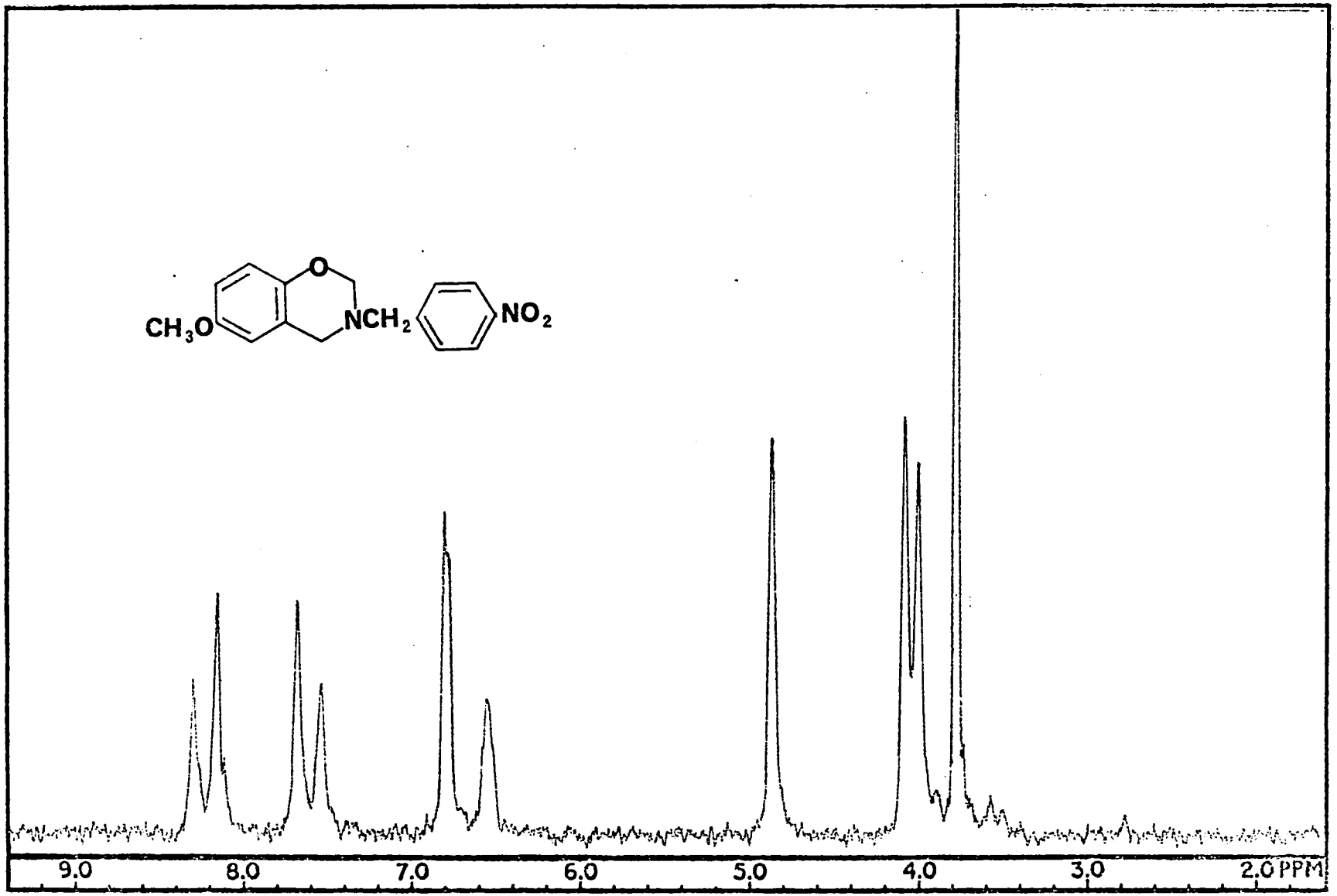
B-14. 2-[β-(4'-Nitrophenyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (45).



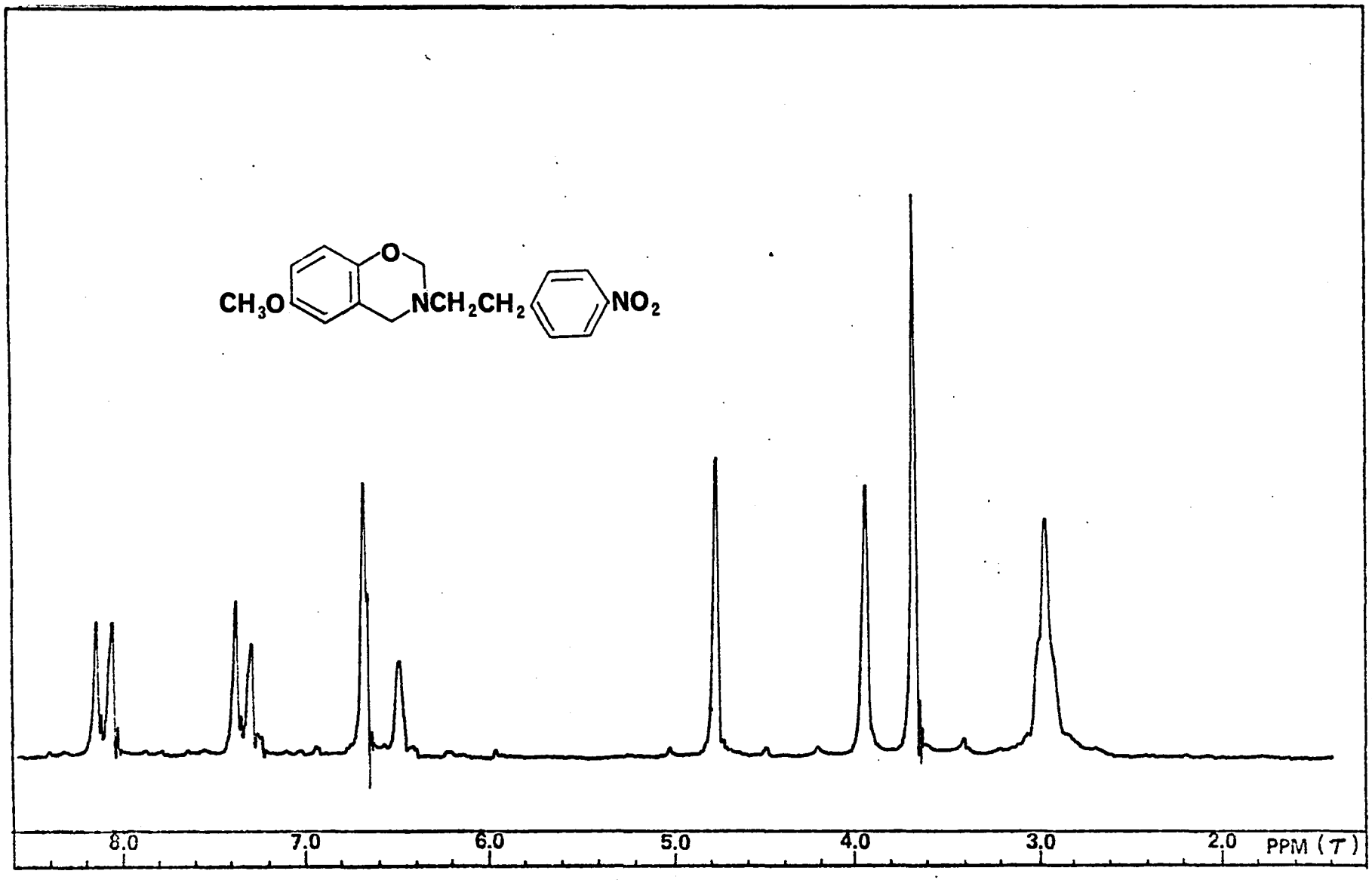
B-15. 2-[β-(4'-Nitrophenyl)ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (52).



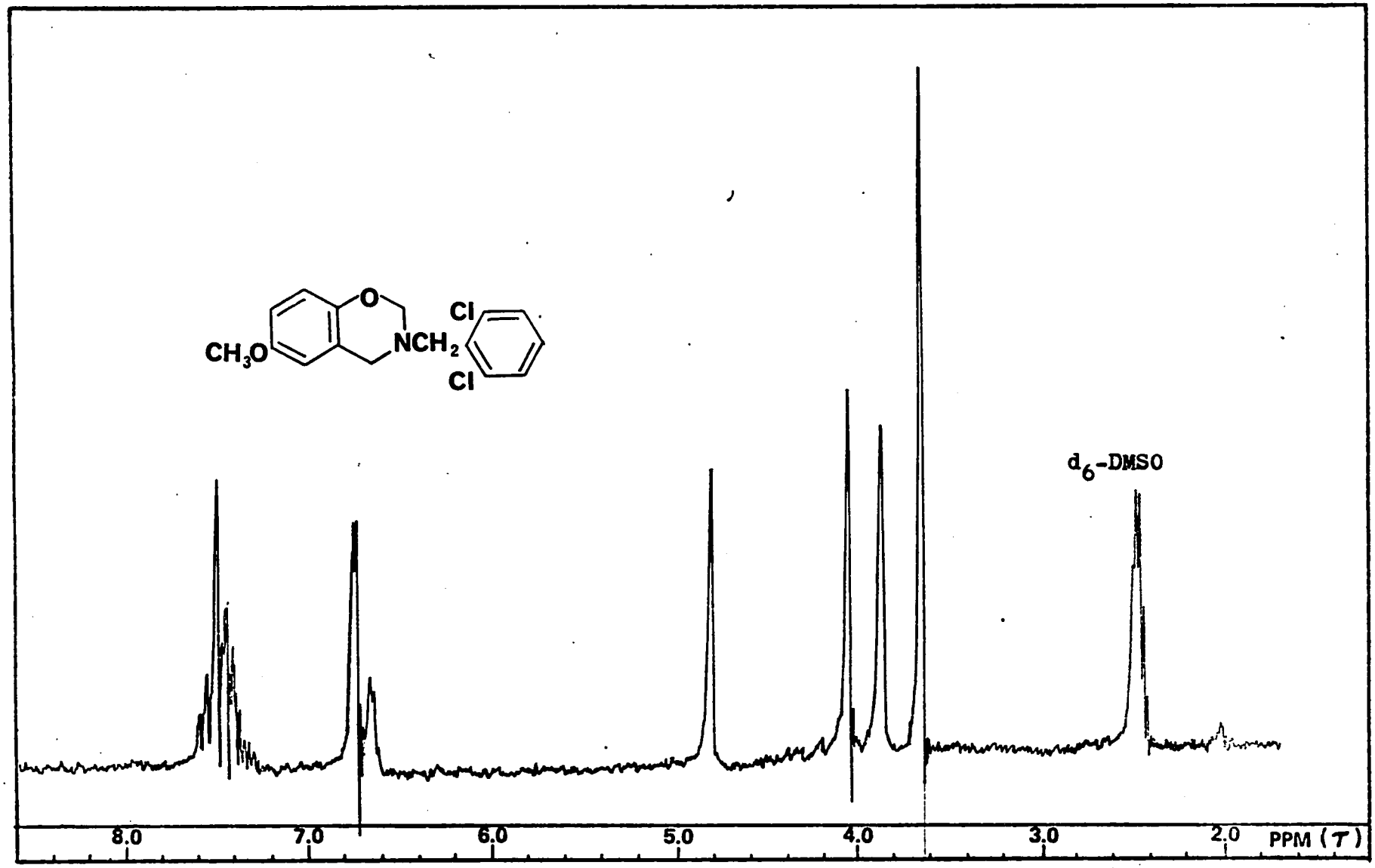
B-16. α,α-Dideutero-2-benzyl-1,2,3,4-tetrahydroisoquinolinium Hydrochloride (61).



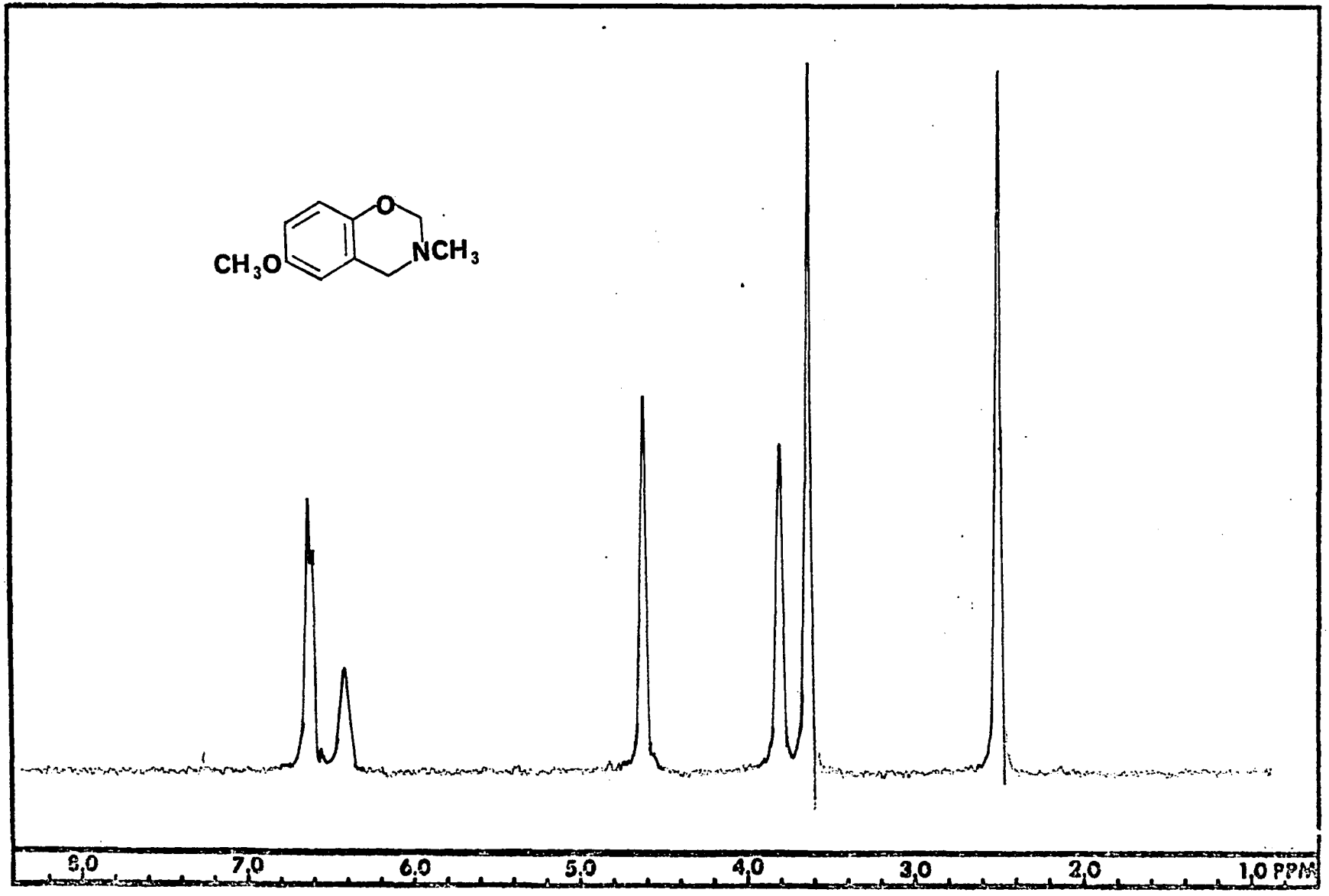
B-17. 3,4-Dihydro-3-(4'-nitrobenzyl)-6-methoxy-1,3,2H-benzoxazine (71).



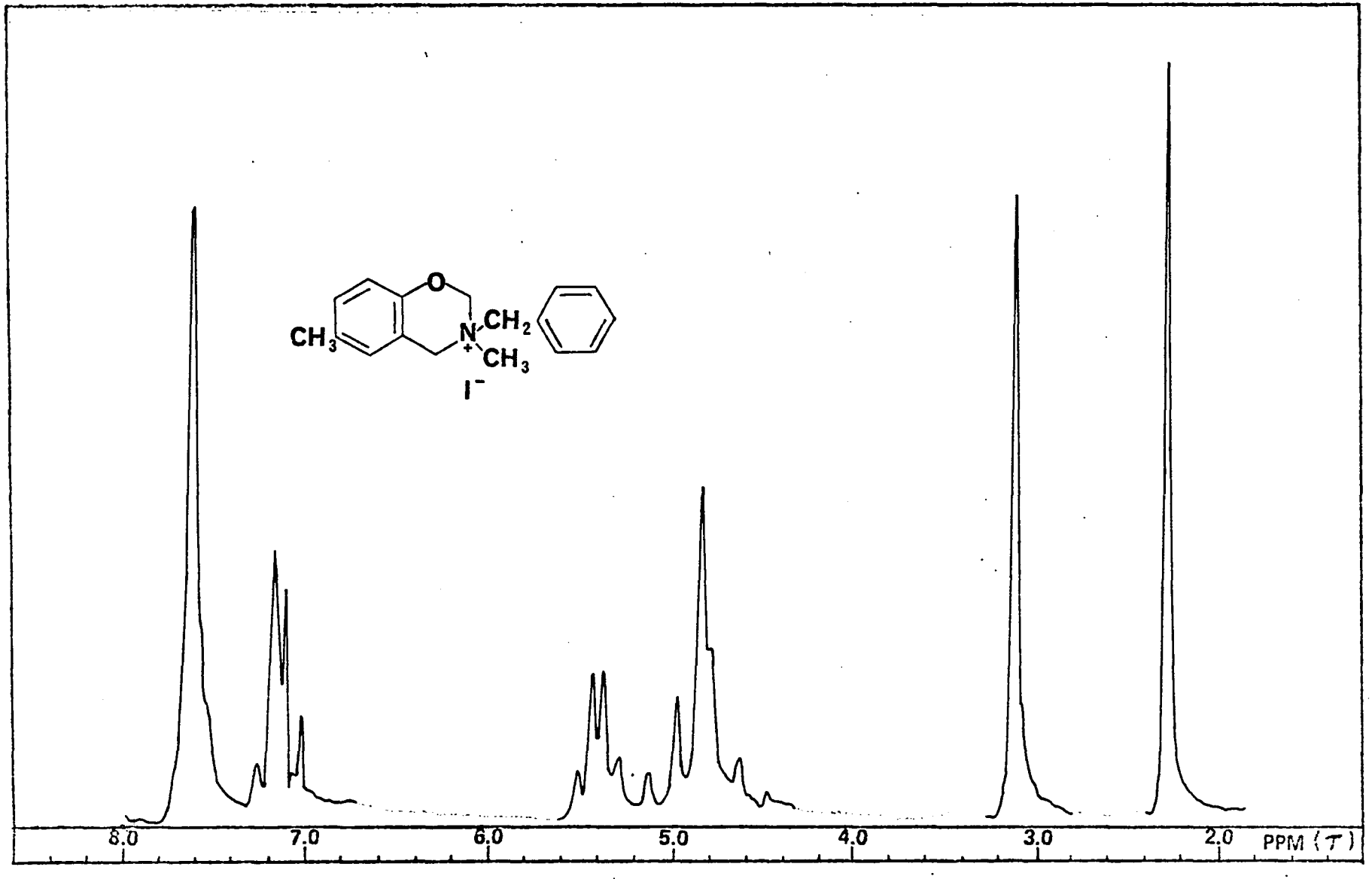
B-18. 3,4-Dihydro-3-[β-(4'-nitrophenyl)ethyl]-6-methoxy-1,3,2H-benzoxazine (73).



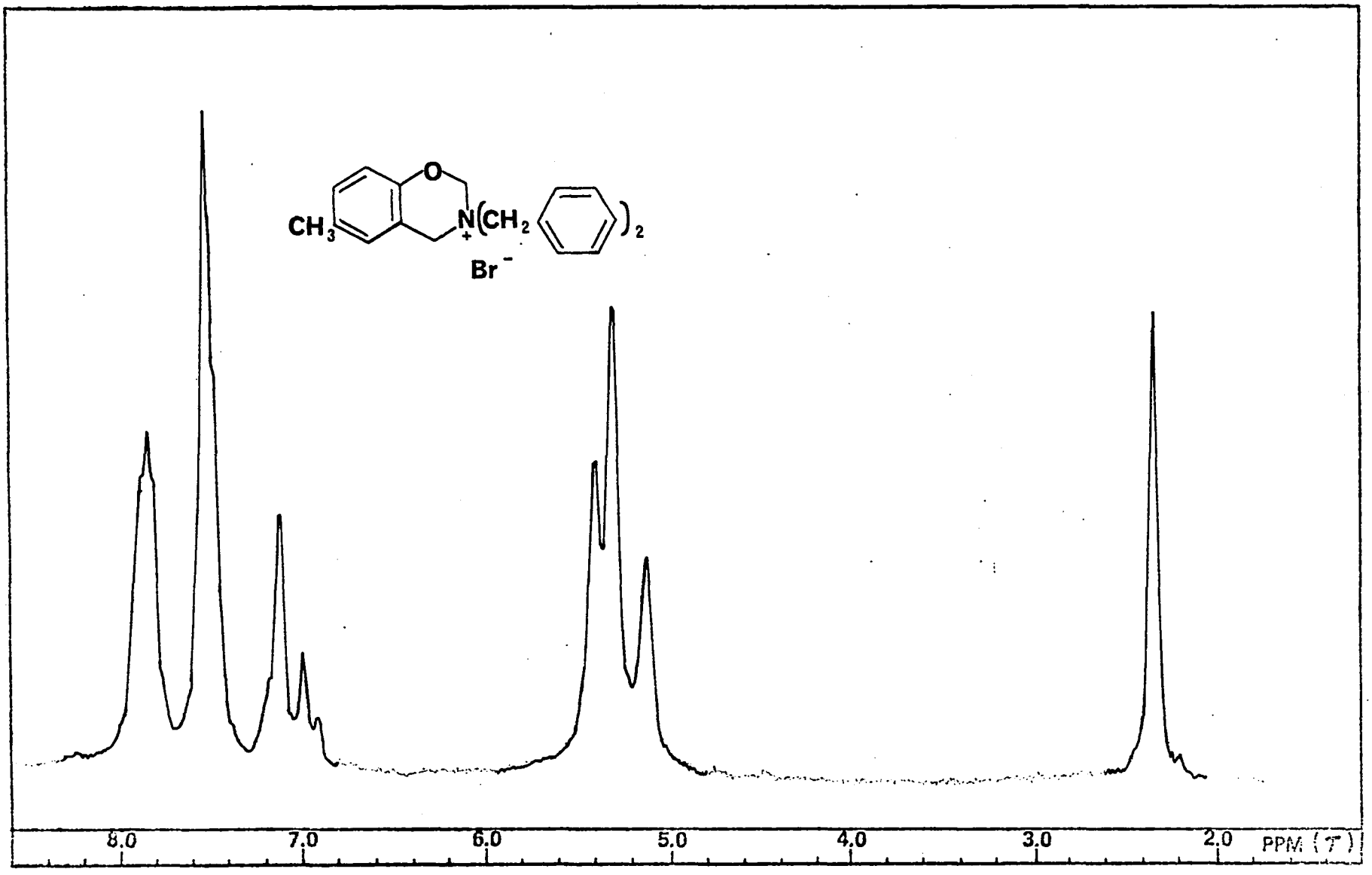
B-19. 3,4-Dihydro-3-(2',6'-dichlorobenzyl)-6-methoxy-1,3,2H-benzoxazine (74).



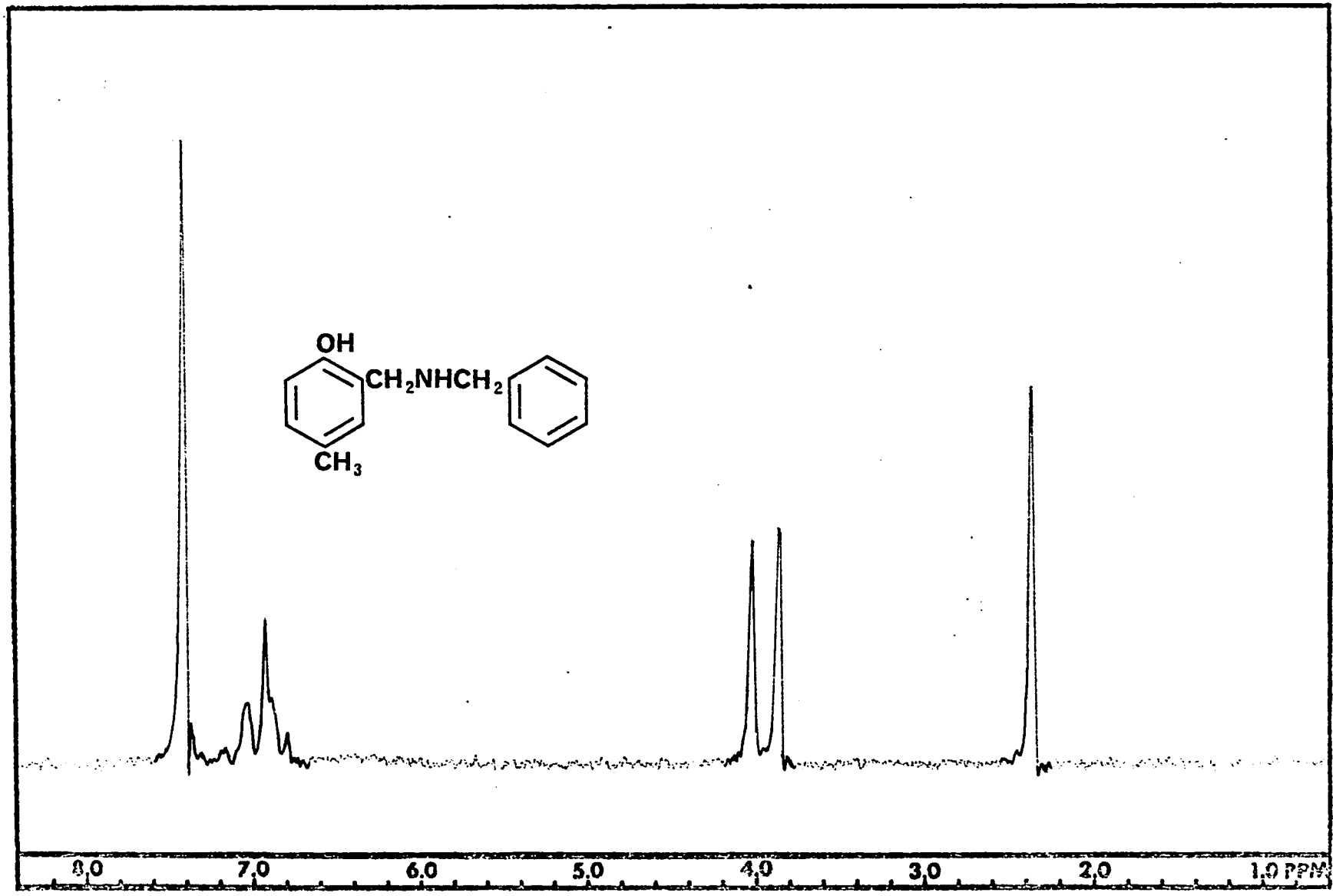
B-20. 3,4-Dihydro-3-methyl-6-methoxy-1,3,2H-benzoxazine (69).



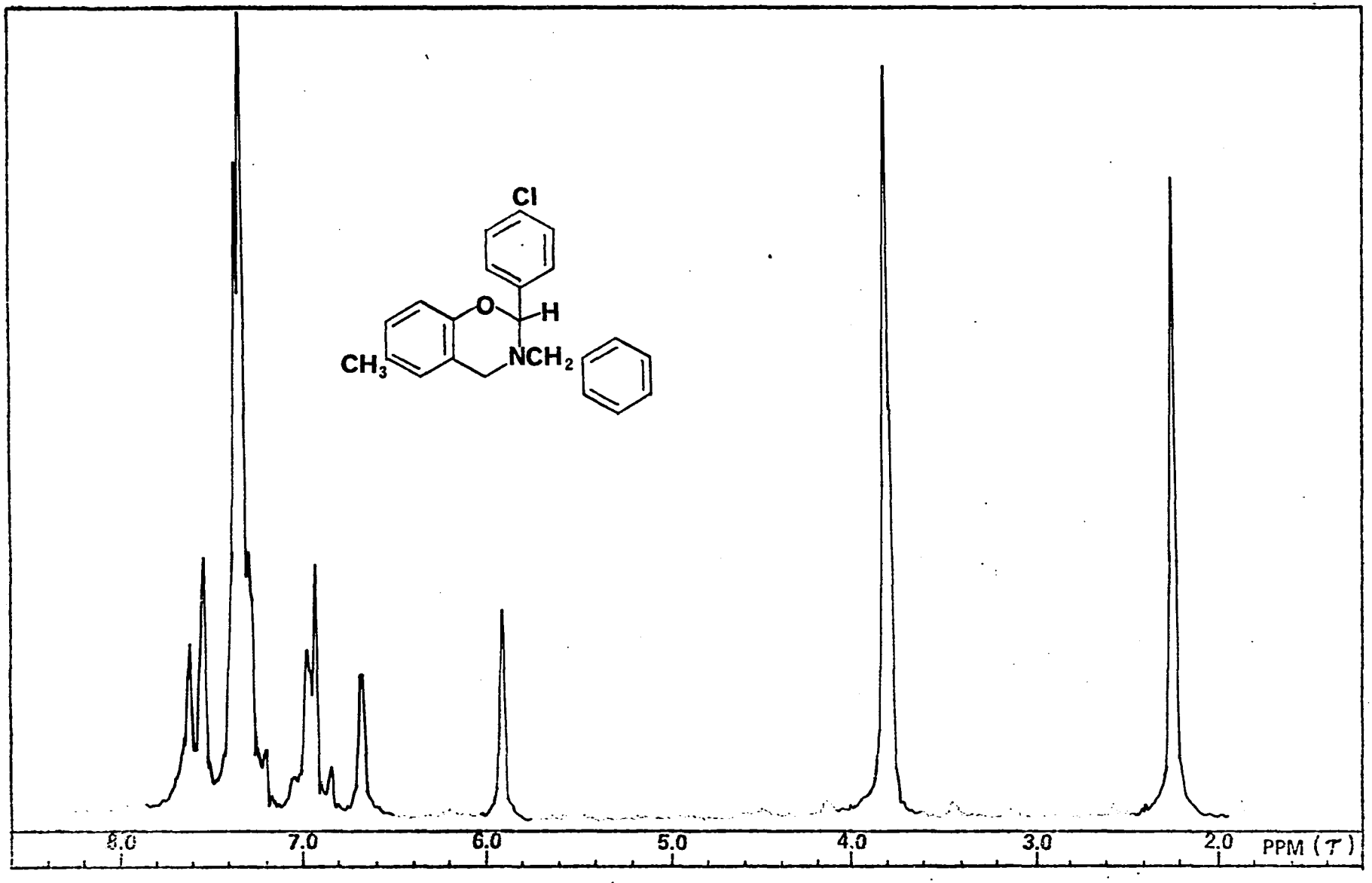
B-21. 3,4-Dihydro-3-benzyl-3,6-dimethyl-1,3,2H-benzoxazinium Iodide (78).



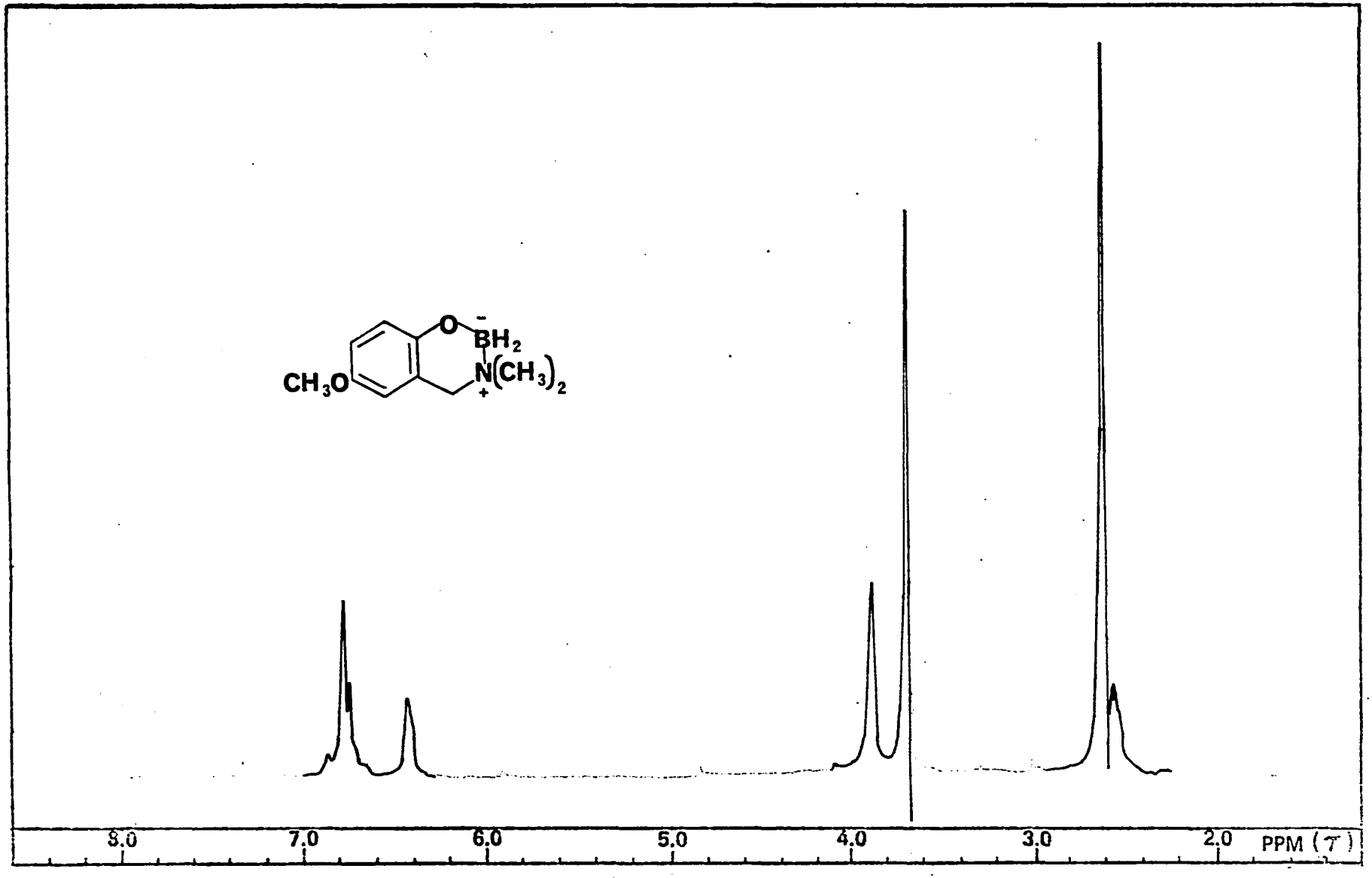
B-22. 3,4-Dihydro-3,4-dibenzyl-6-methyl-1,3,2H-benzoxazinium Bromide (79).



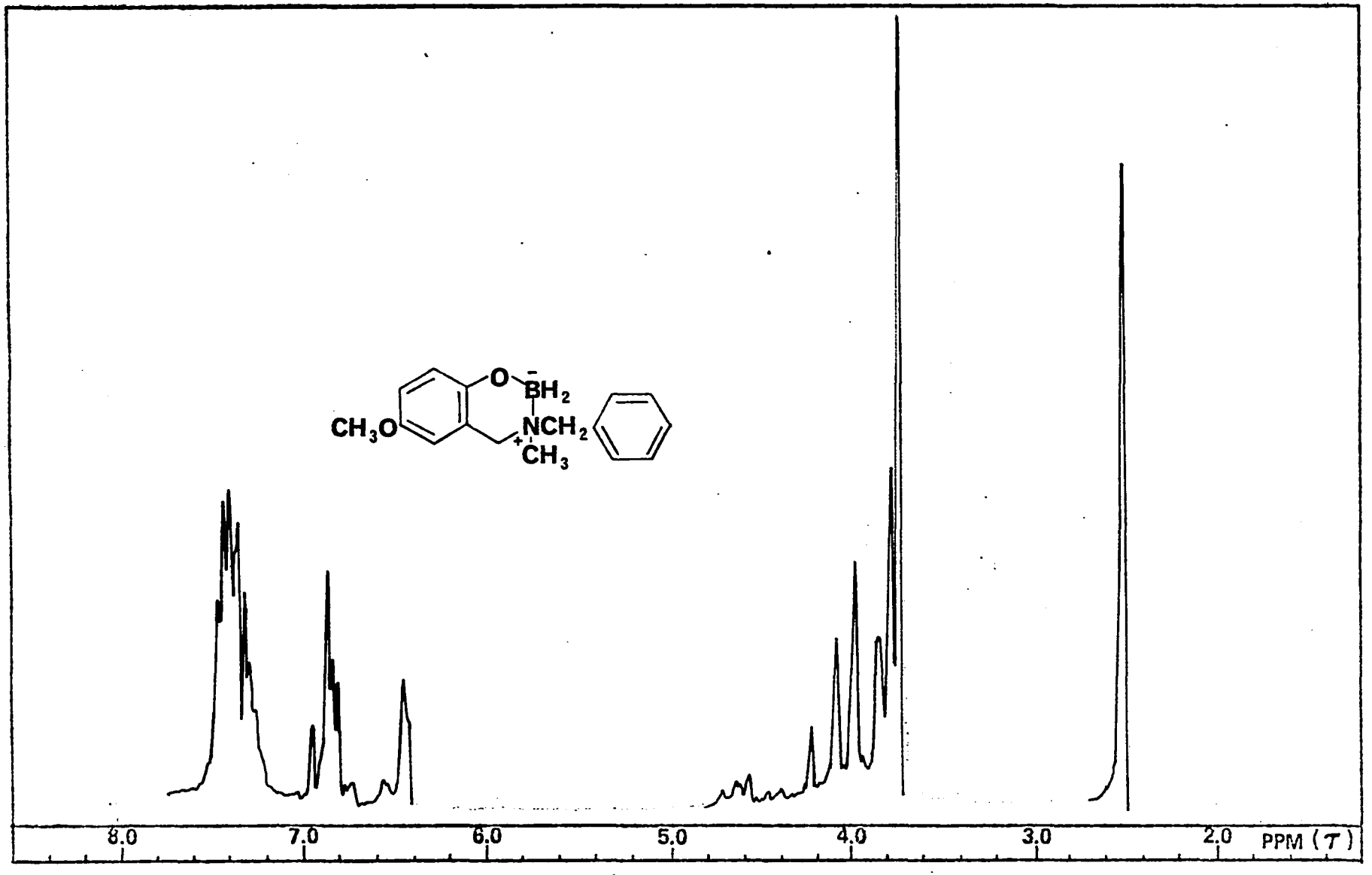
B-23. 2-(Benzylaminomethyl)-4-methylphenol (77).



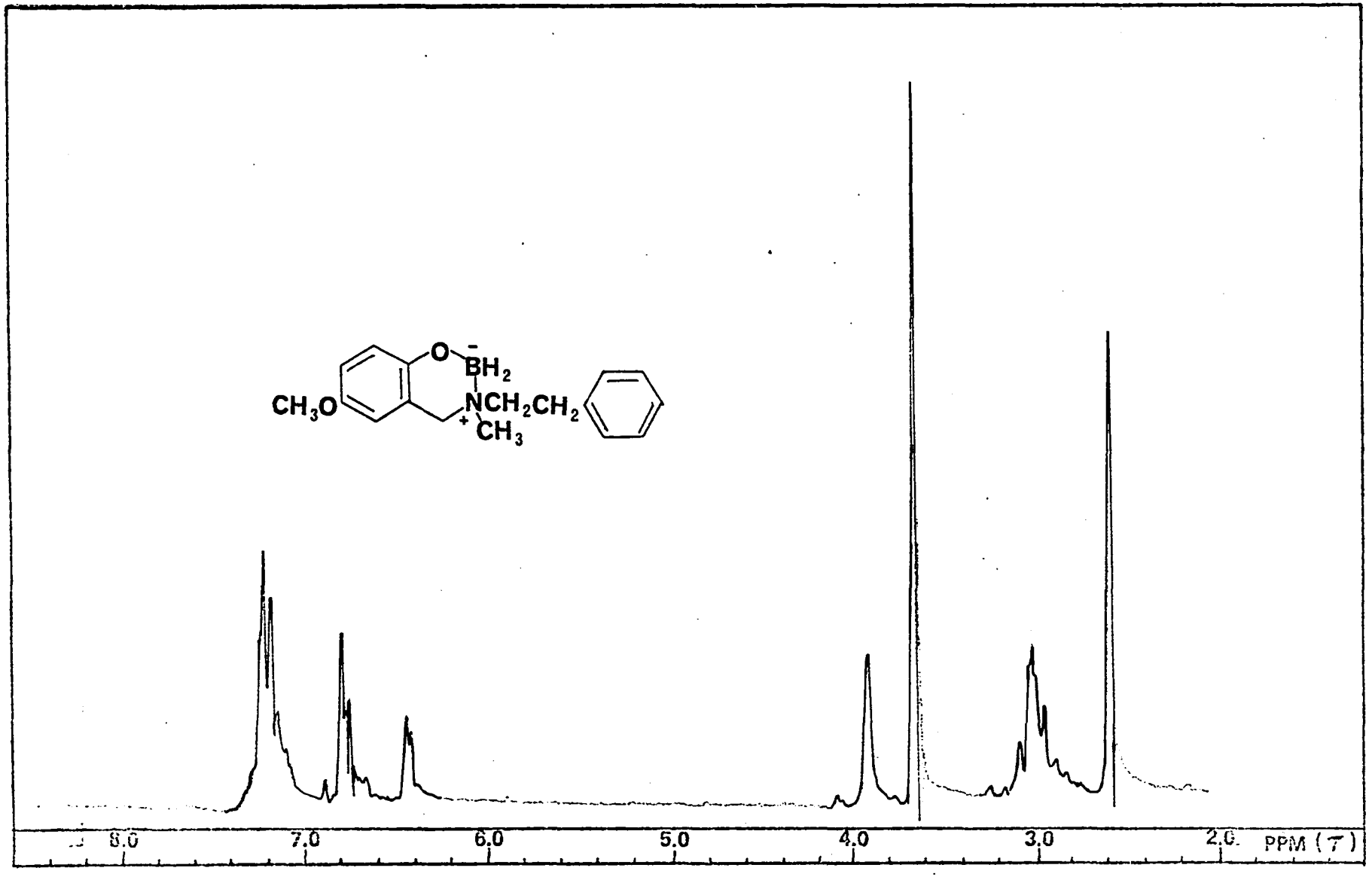
B-24. 3,4-Dihydro-2-p-Chlorophenyl-3-benzyl-6-methyl-1,3,2H-benzoxazine (76).



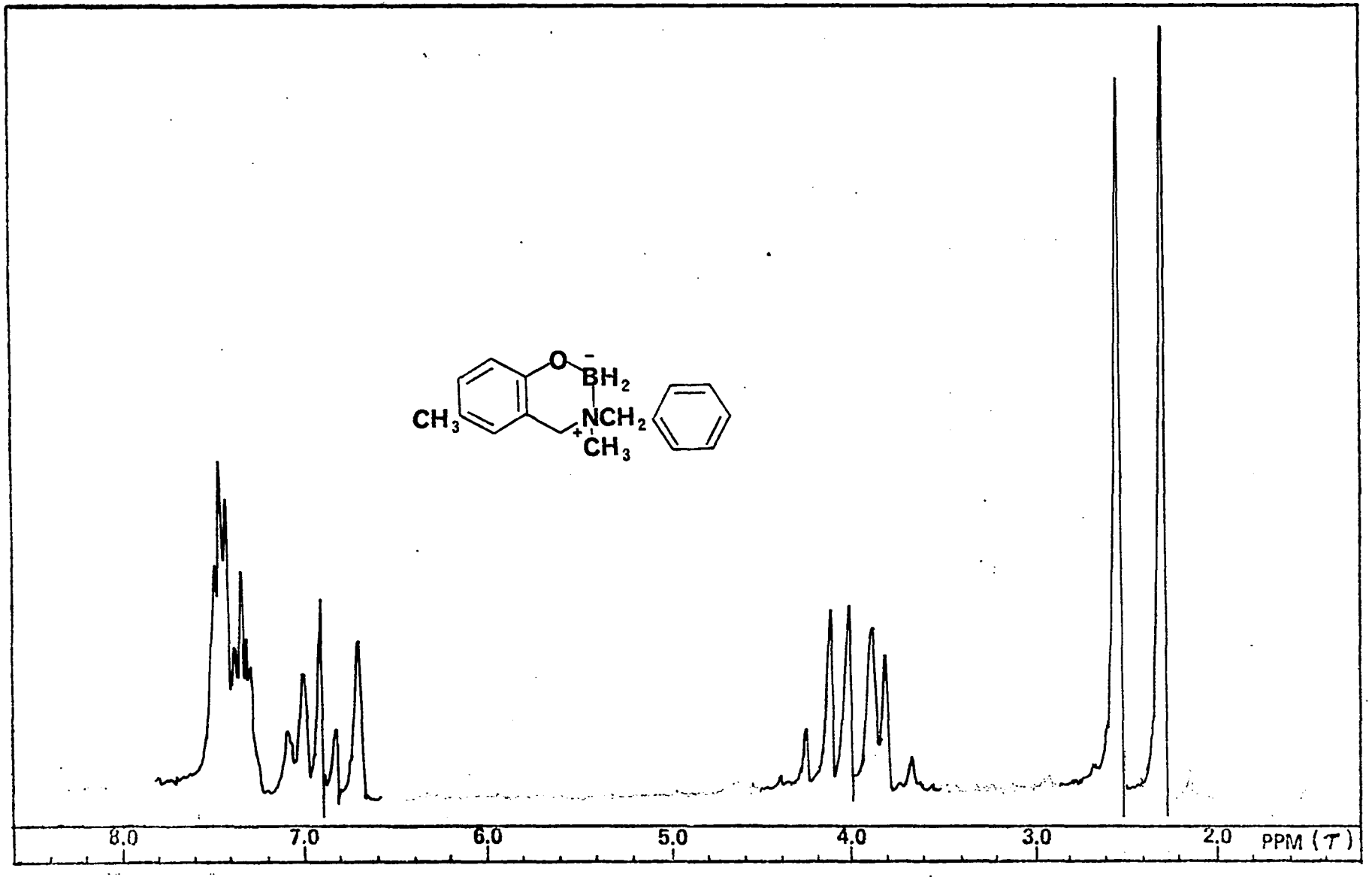
B-25. 3,3-Dimethyl-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (85).



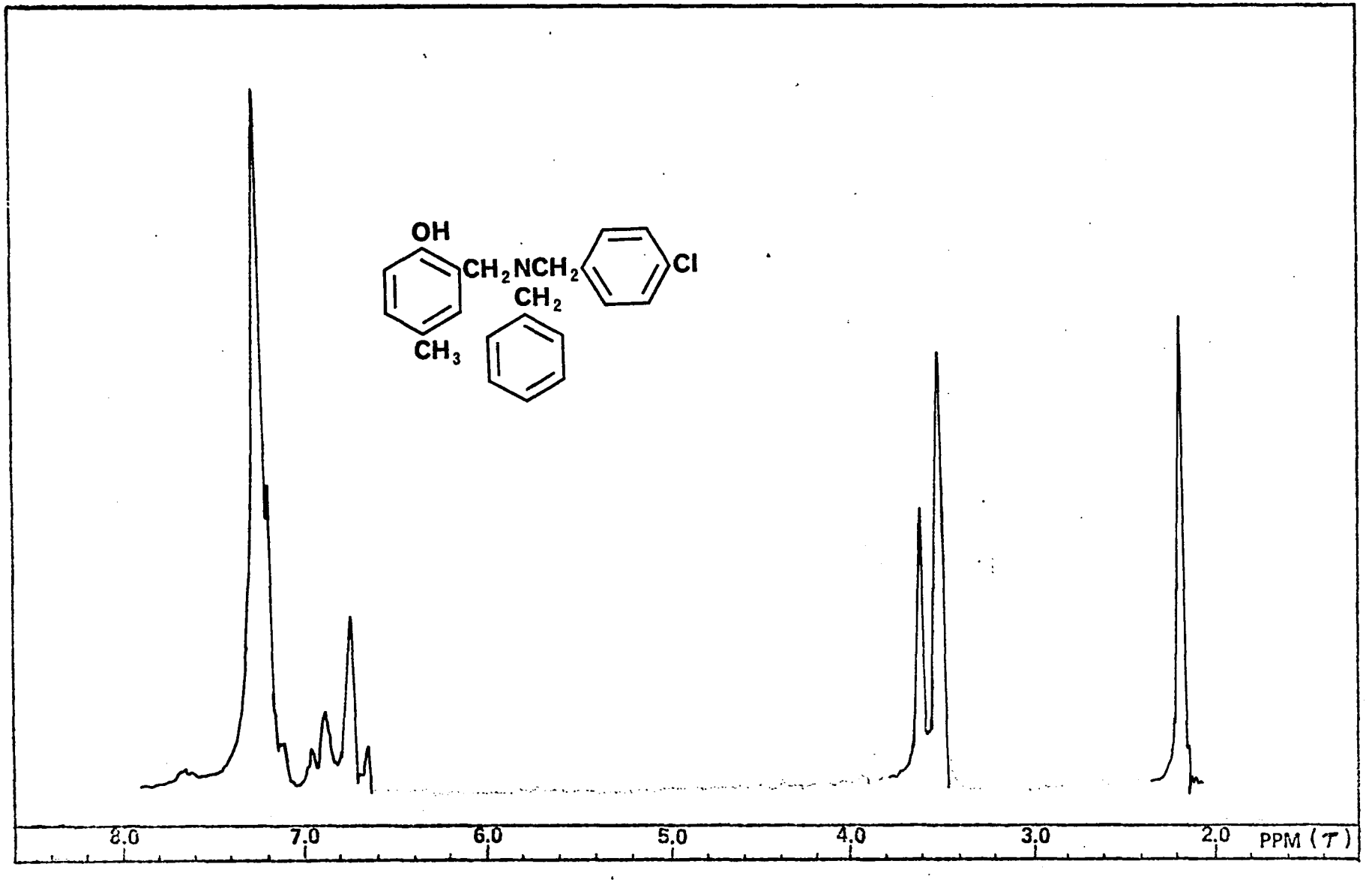
B-26. 3-Benzyl-3-methyl-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (86).



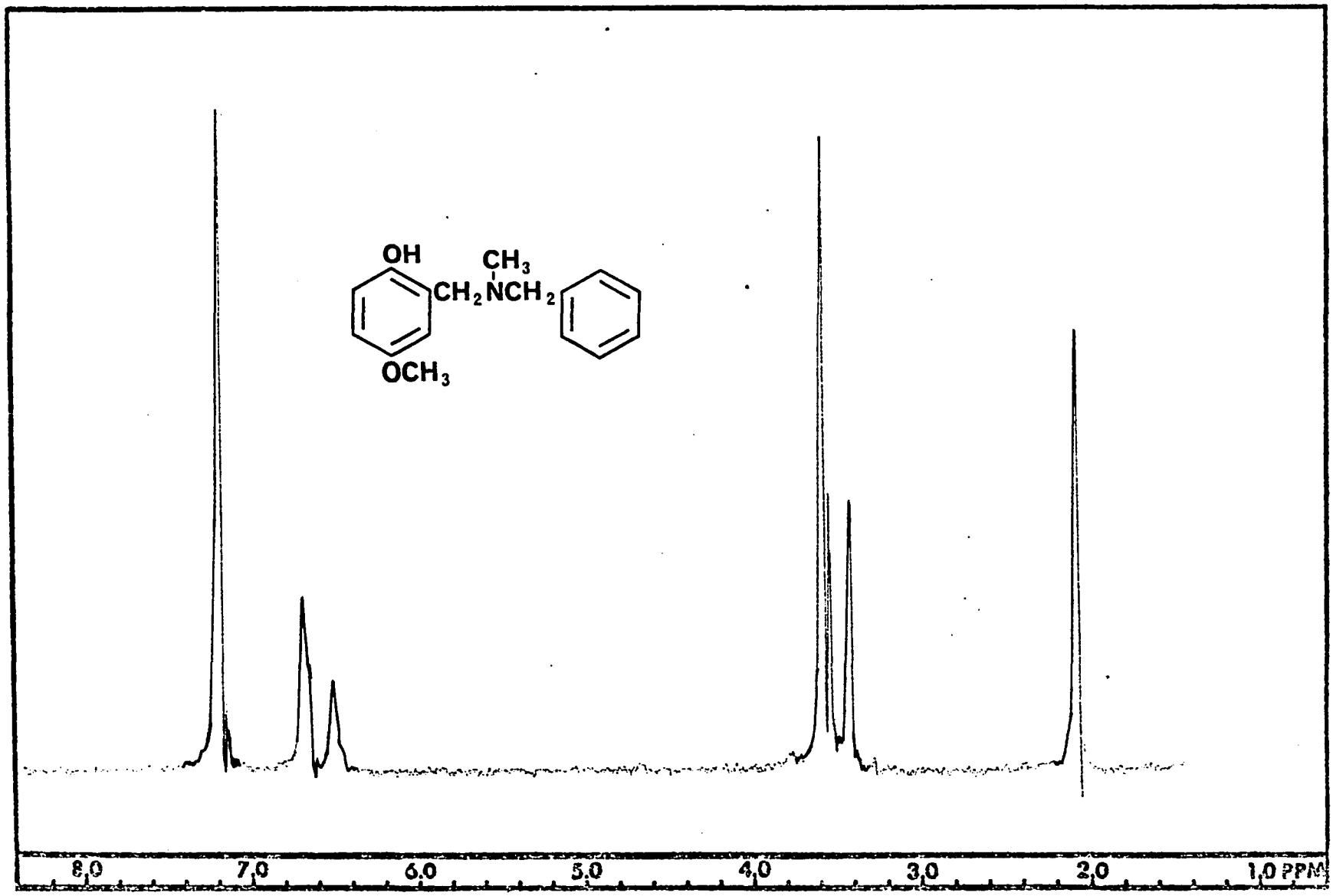
B-27. 3-Methyl-3-(β-phenethyl)-6-methoxy[4H]-1-oxa-3-azonia-2-boratanaphthalene (87).



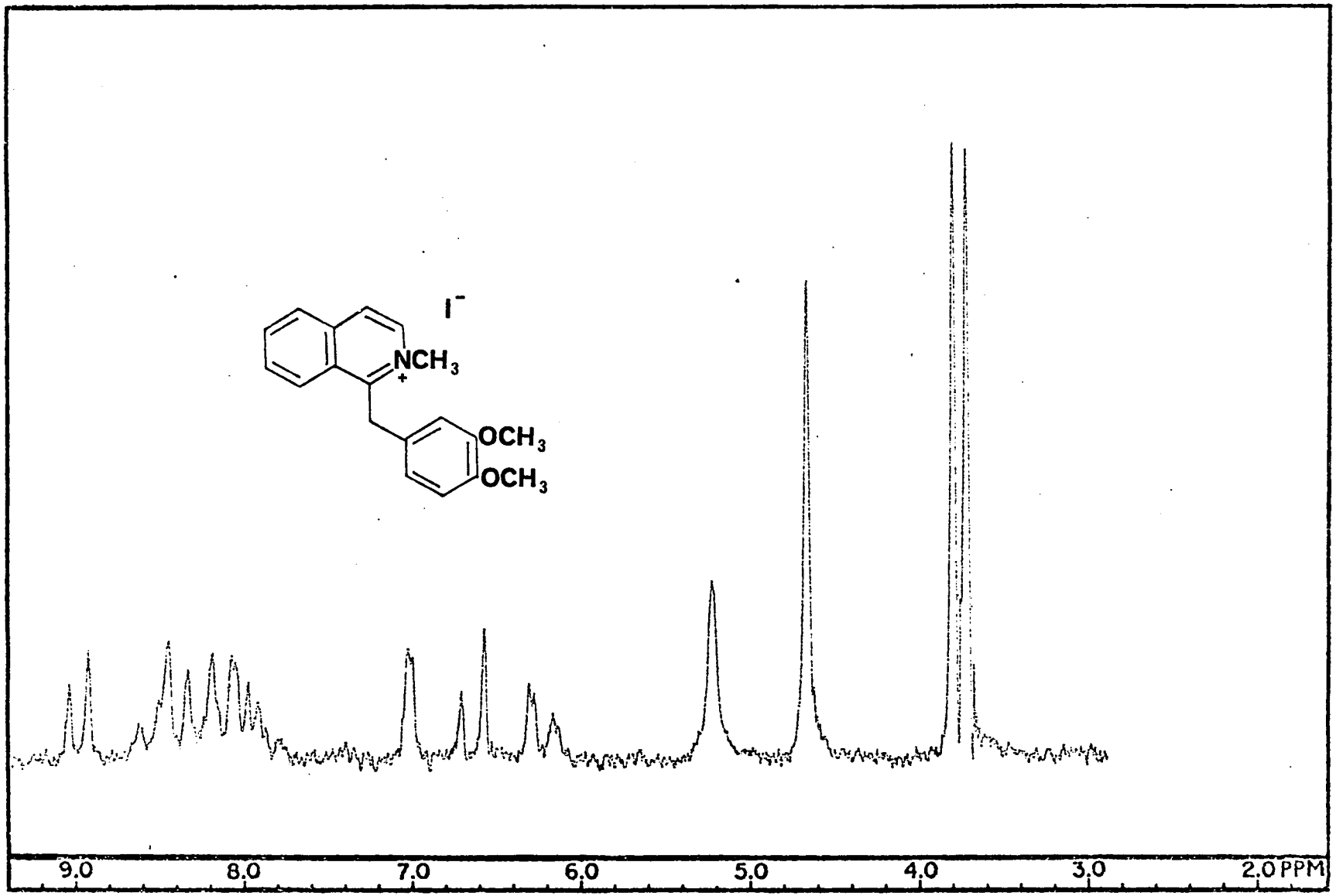
B-28. 3-Benzyl-3,6-dimethyl[4H]-1-oxa-3-azonia-2-boratanaphthalene (88).



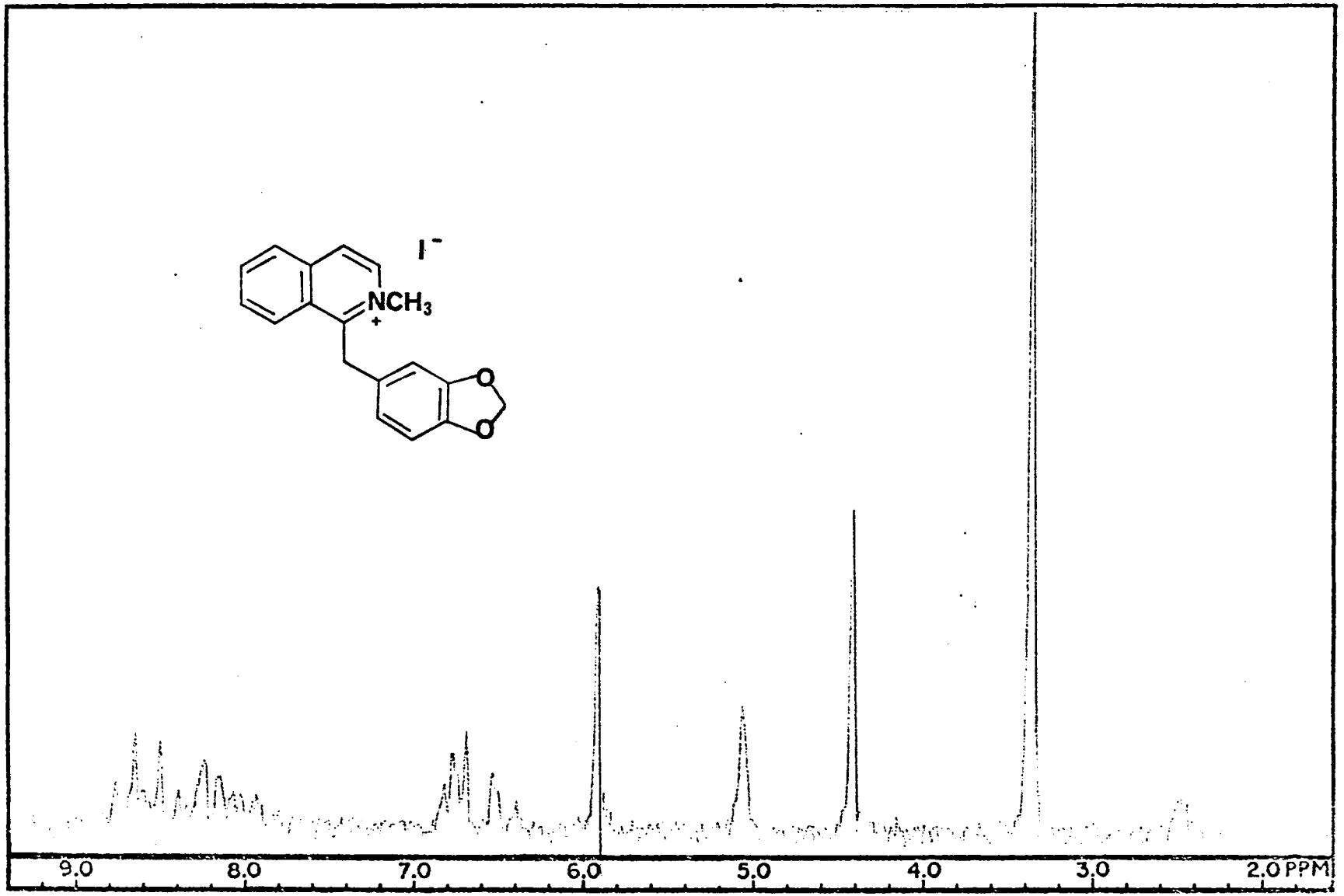
B-29. 2-(Benzyl-p-chlorobenzylaminomethyl)-4-methylphenol (90).



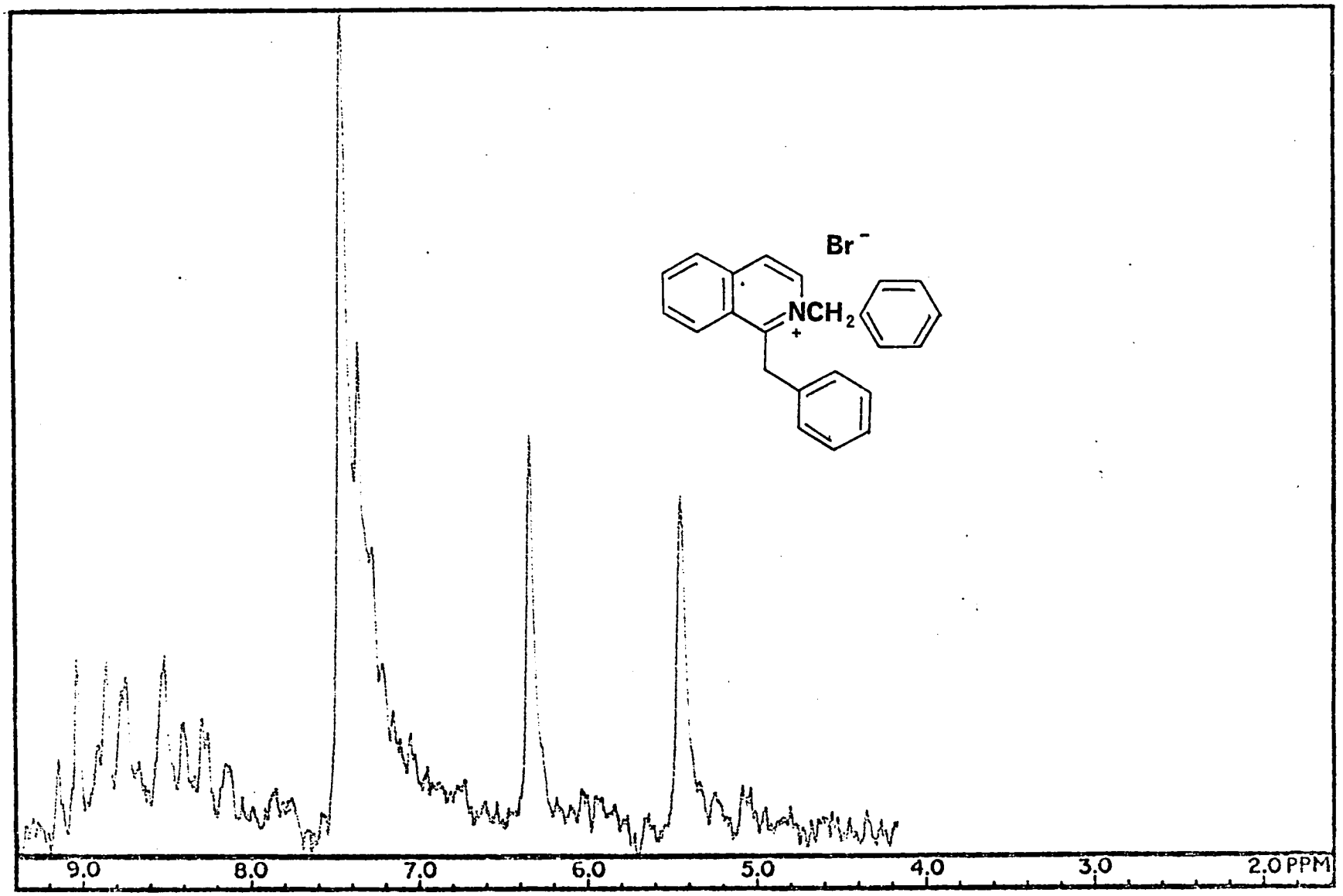
B-30. 2-(Benzylmethylaminomethyl)-4-methoxyphenol (91).



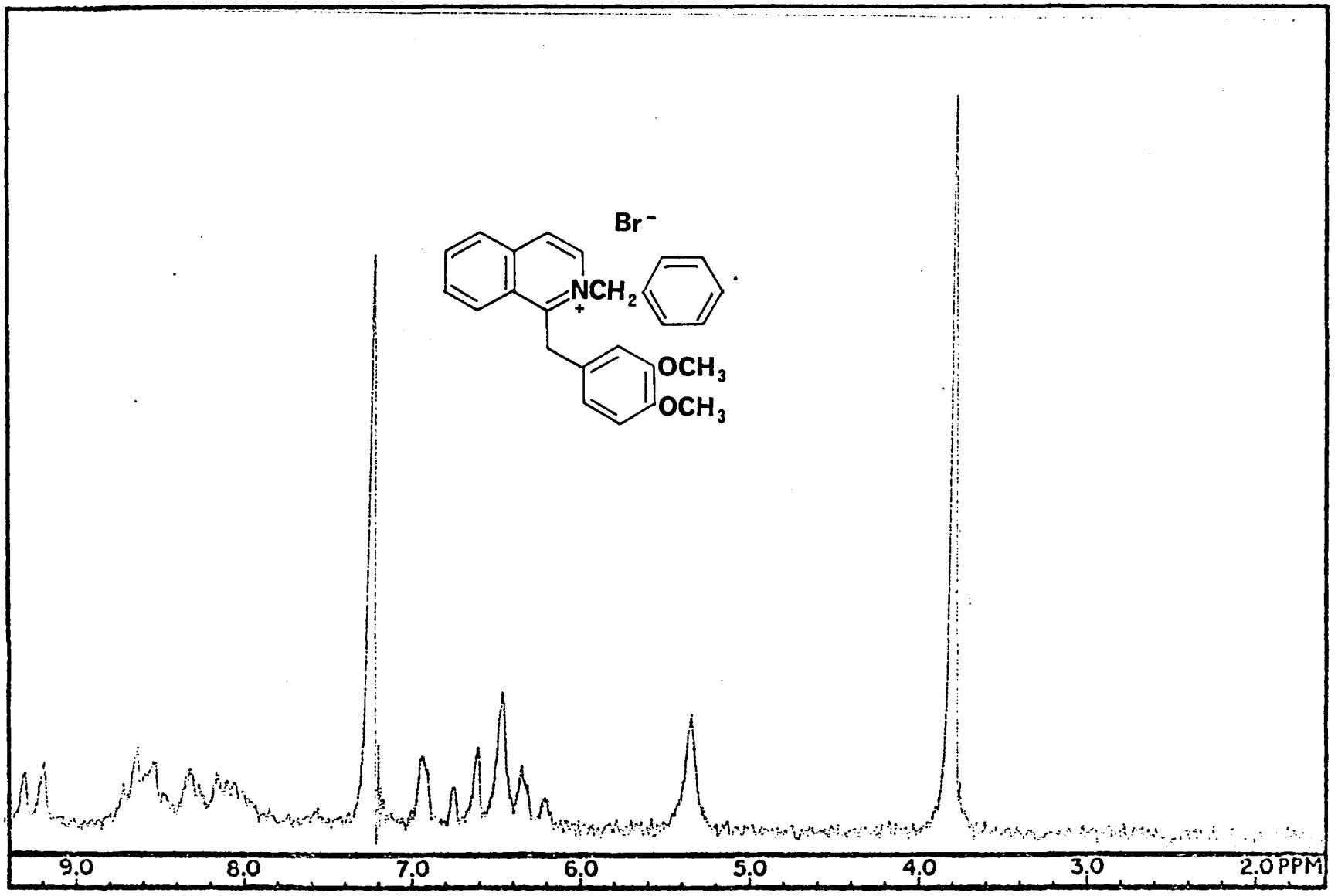
B-31. 1-(3',4'-Dimethoxybenzyl)-2-methylisoquinolinium Iodide (112).



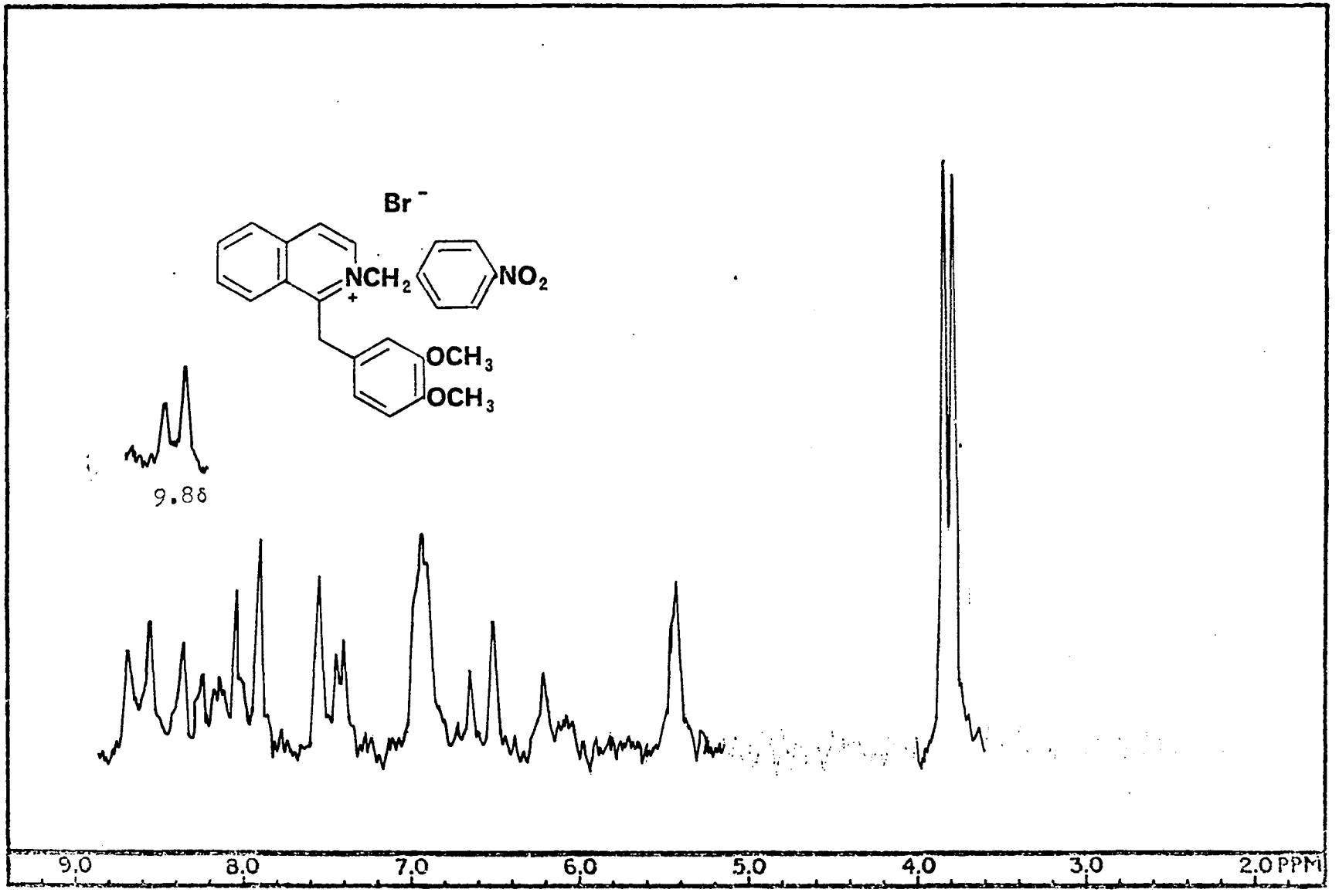
B-32. 1-(3',4'-Methylenedioxybenzyl)-2-methylisoquinolinium Iodide (113).



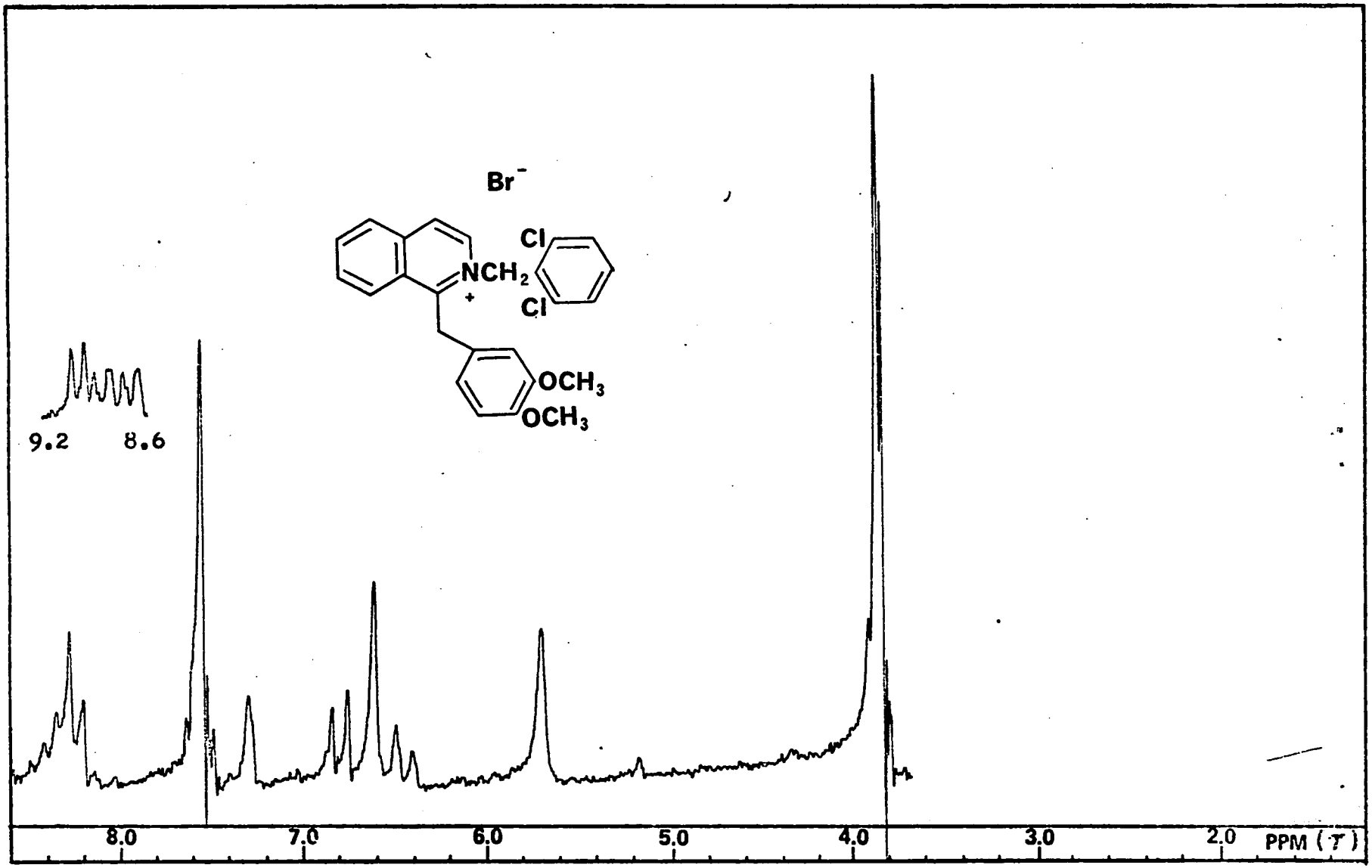
B-33. 1,2-Dibenzylisoquinolinium Bromide (114).



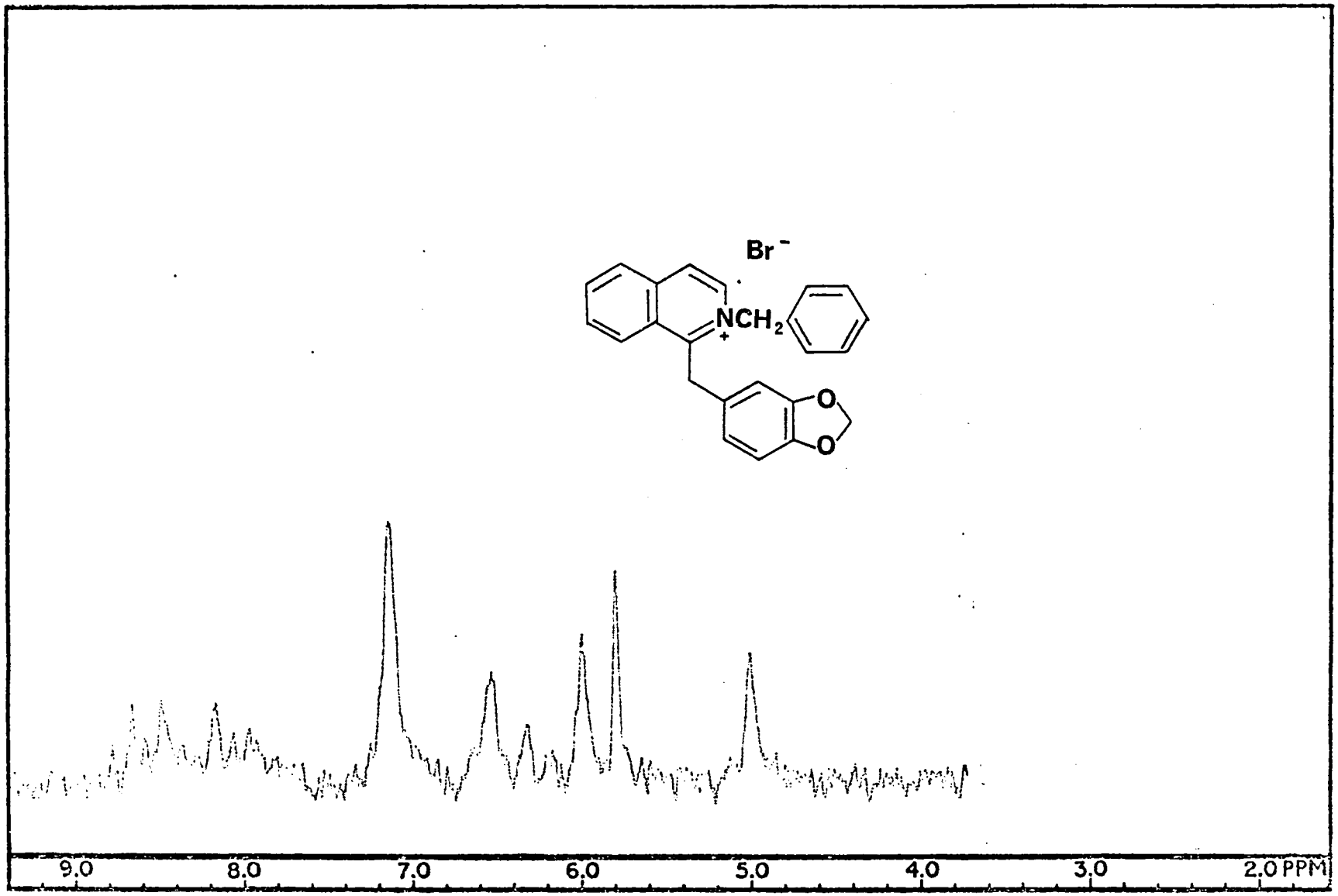
B-34. 1-(3',4'-Dimethoxybenzyl)-2-benzylisoquinolinium Bromide (115).



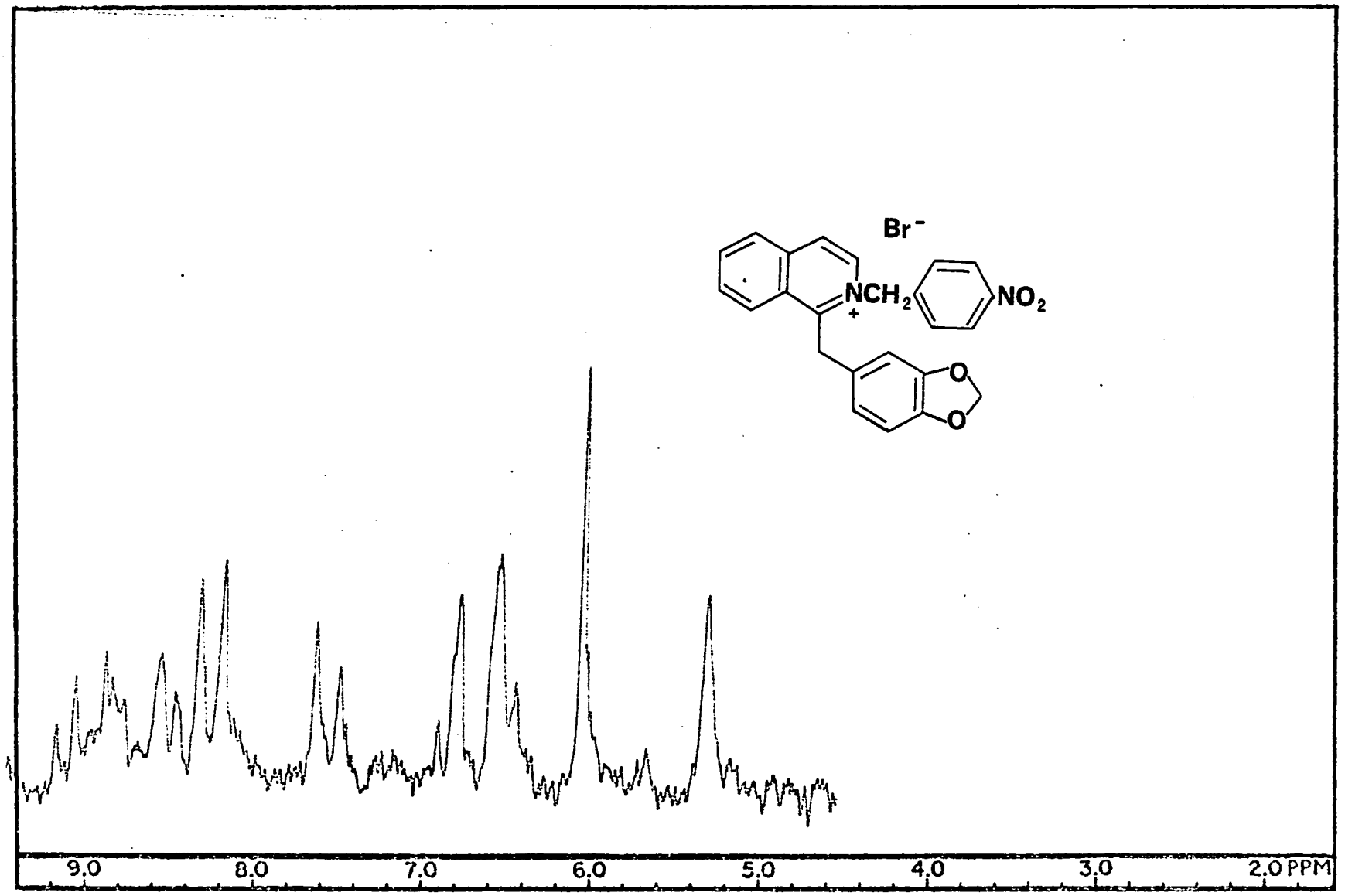
B-35. 1-(3'.4'-Dimethoxybenzyl)-2-(4"-nitrobenzyl)isoquinolinium Bromide (116).



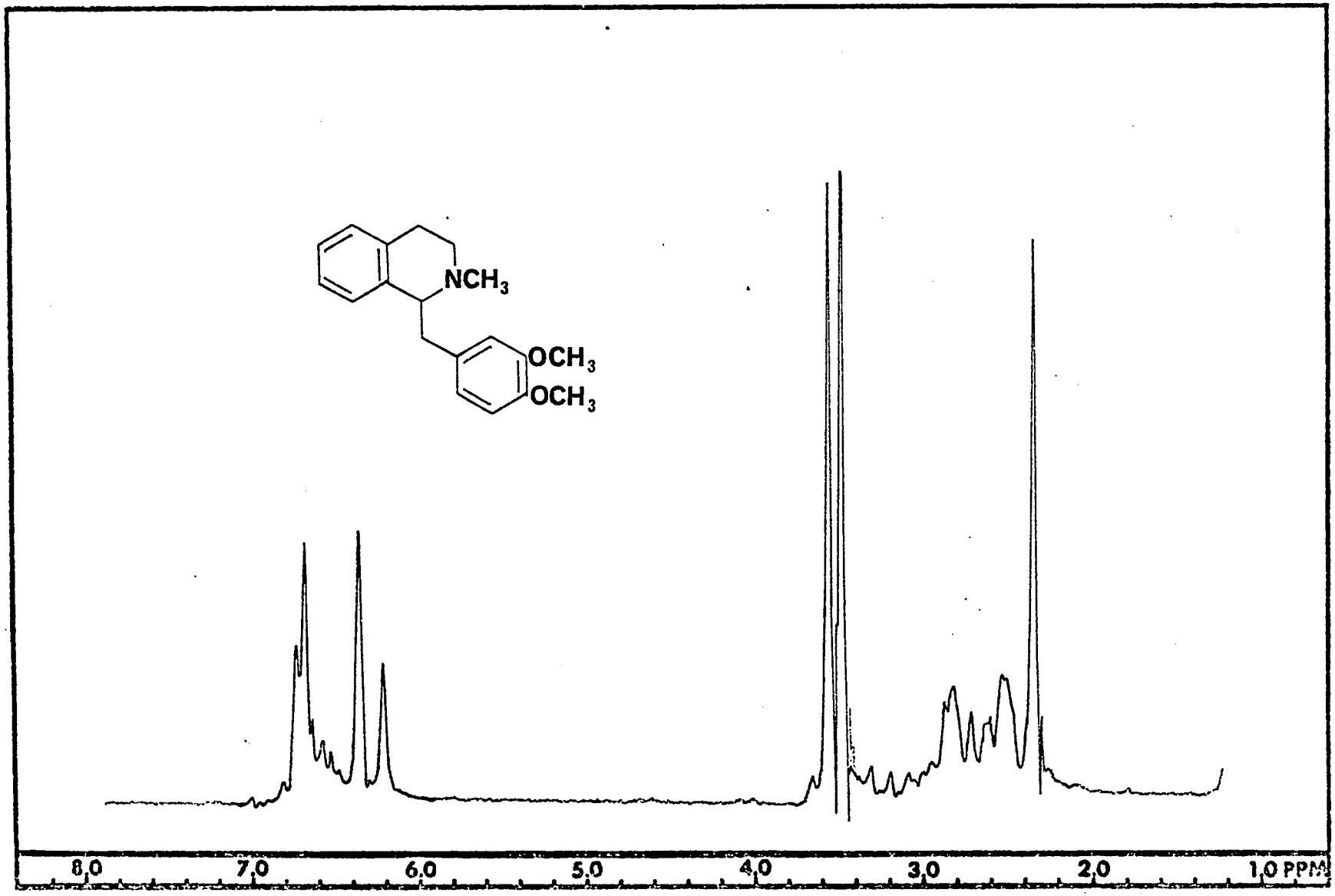
B-36. 1-(3',4'-Dimethoxybenzyl)-2-(2",6"-dichlorobenzyl)isoquinolinium Bromide (117).



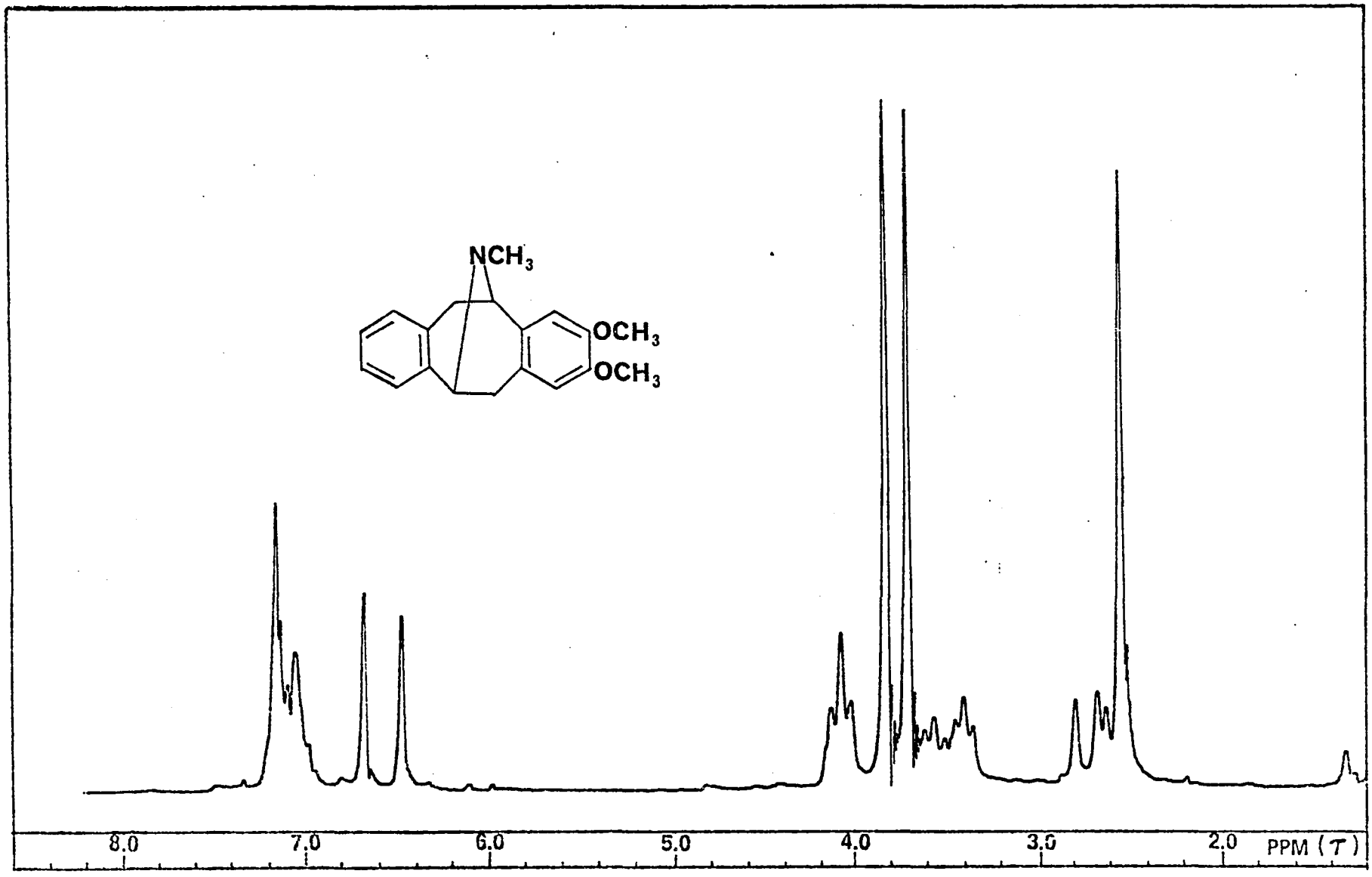
B-37. 1-(3',4'-Methylenedioxybenzyl)-2-benzylisoquinolinium Bromide (118).



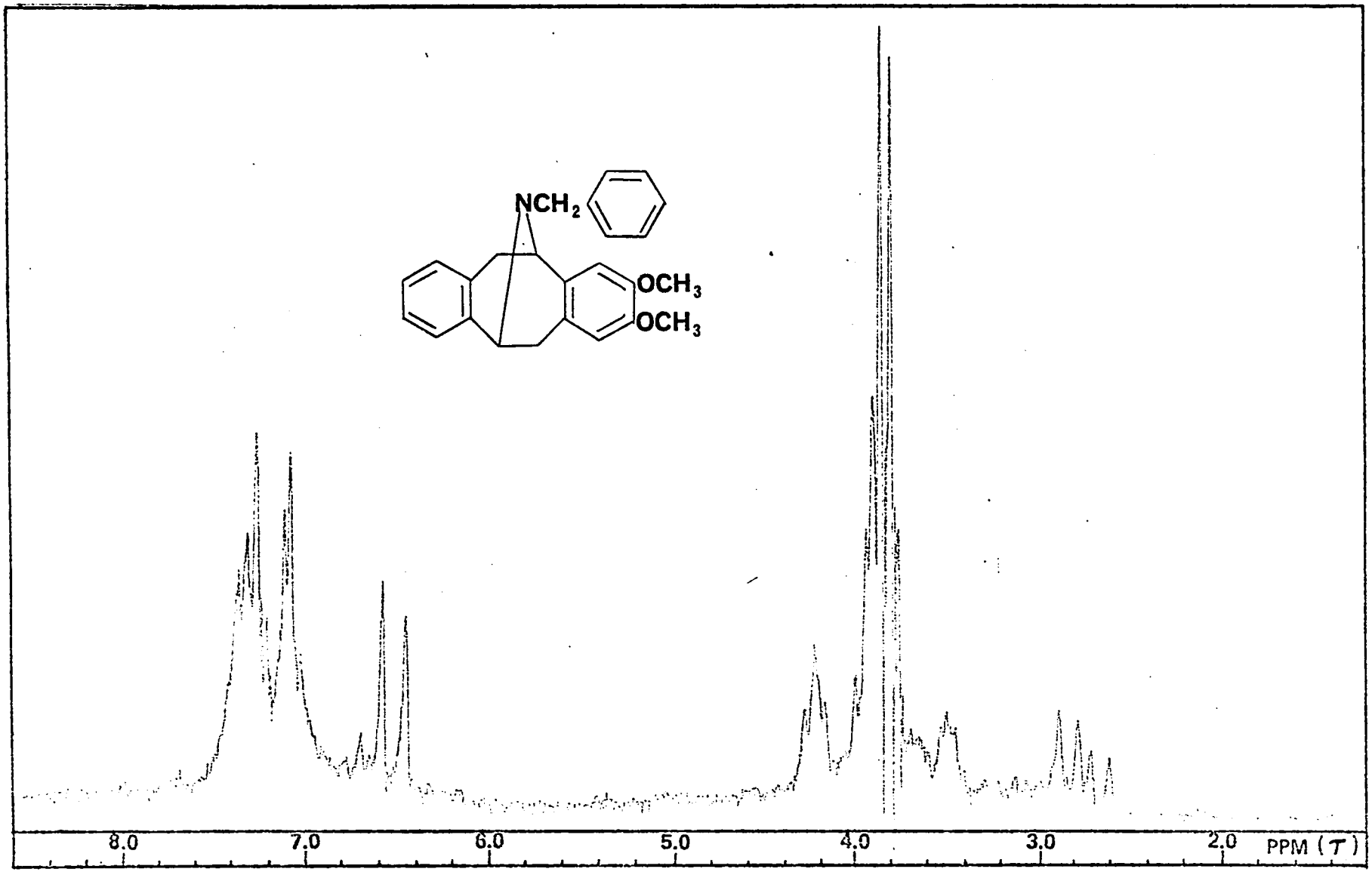
B-38. 1-(3',4'-Methylenedioxybenzyl)-2-(4"-nitrobenzyl)isoquinolinium Bromide (119).



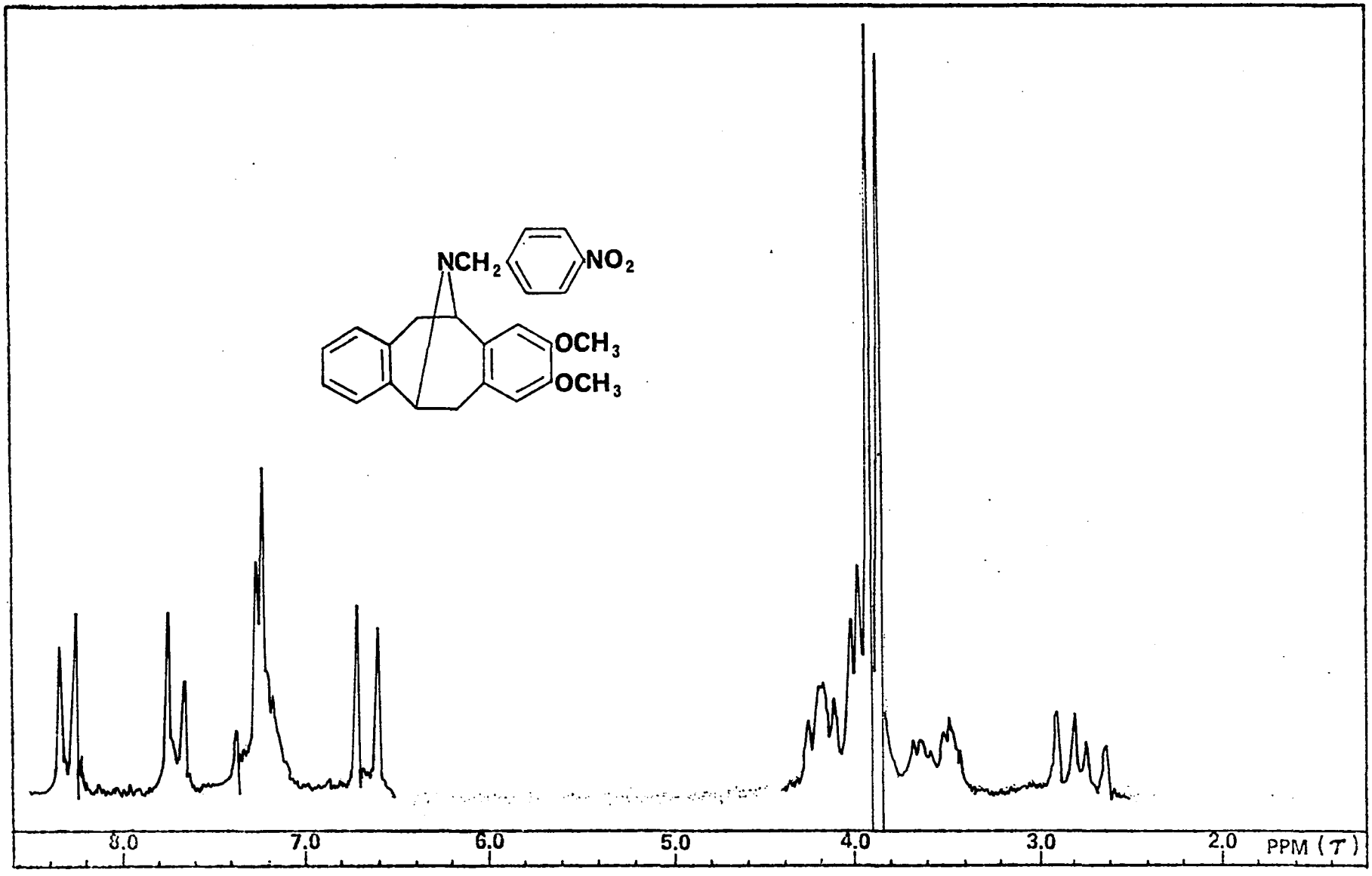
B-39. 1-(3',4'-Dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (120).



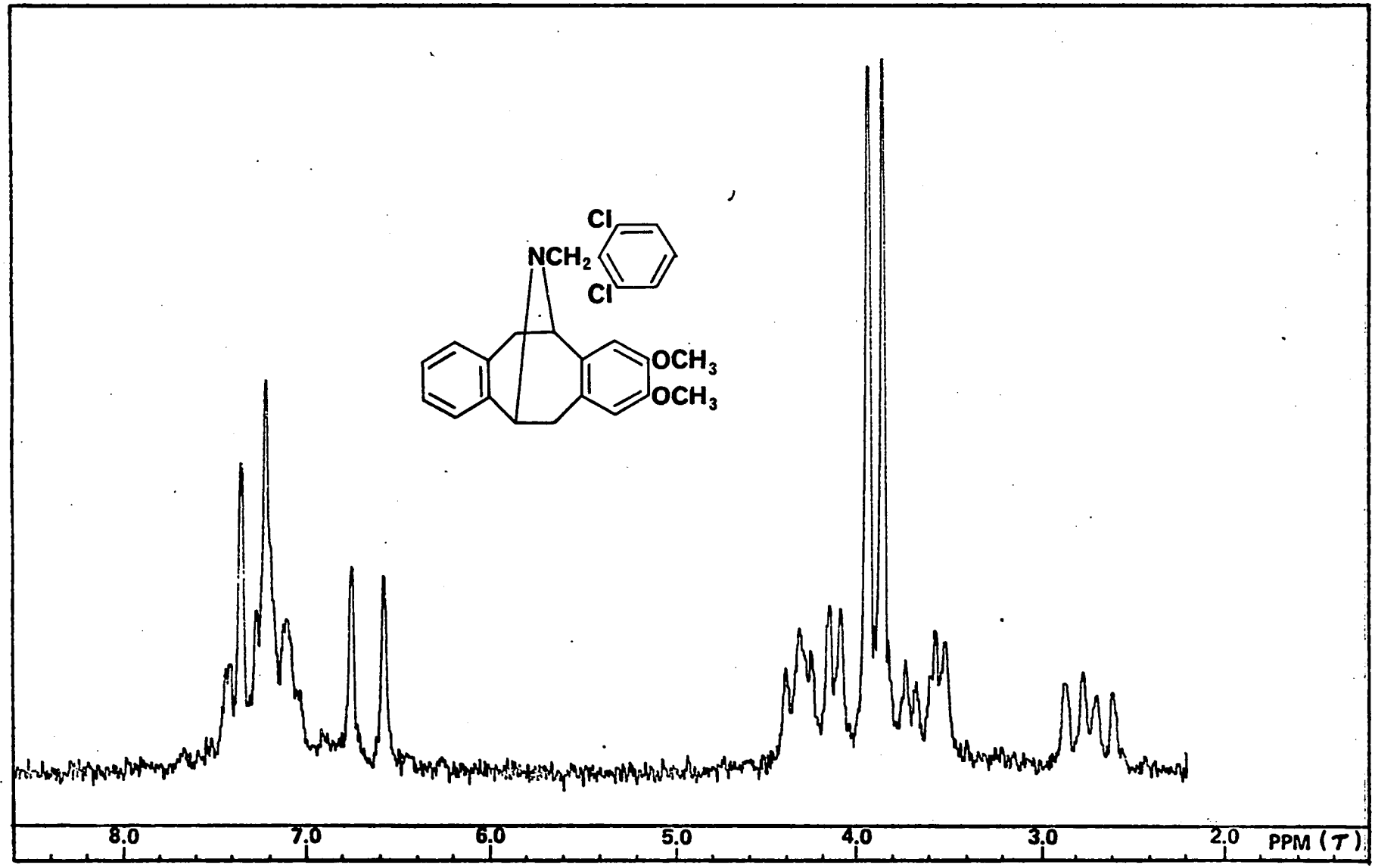
B-40. 2,3-Dimethoxy-N-methylpavinane (128).



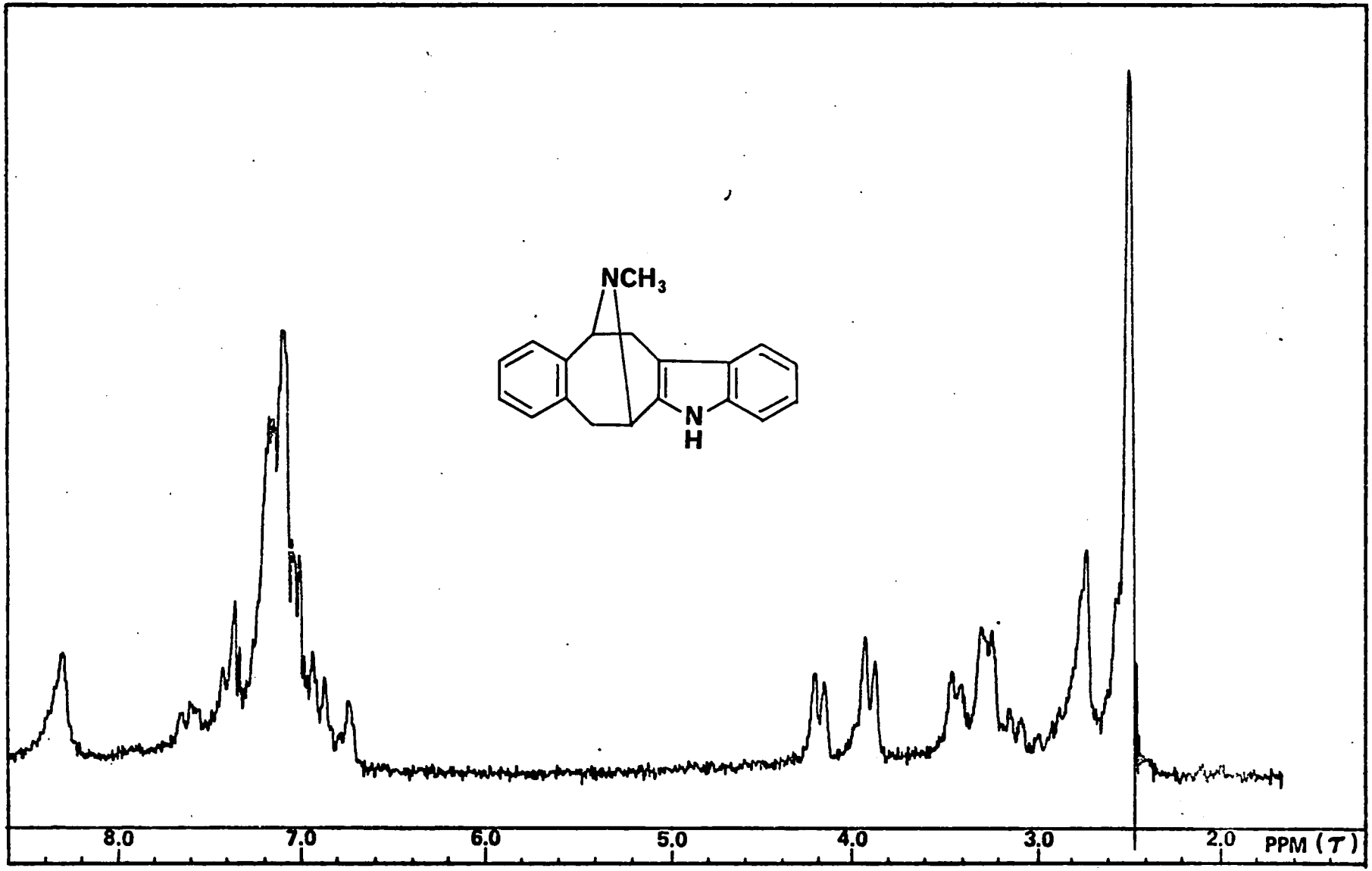
B-41. 2,3-Dimethoxy-N-benzylpavinane (129).



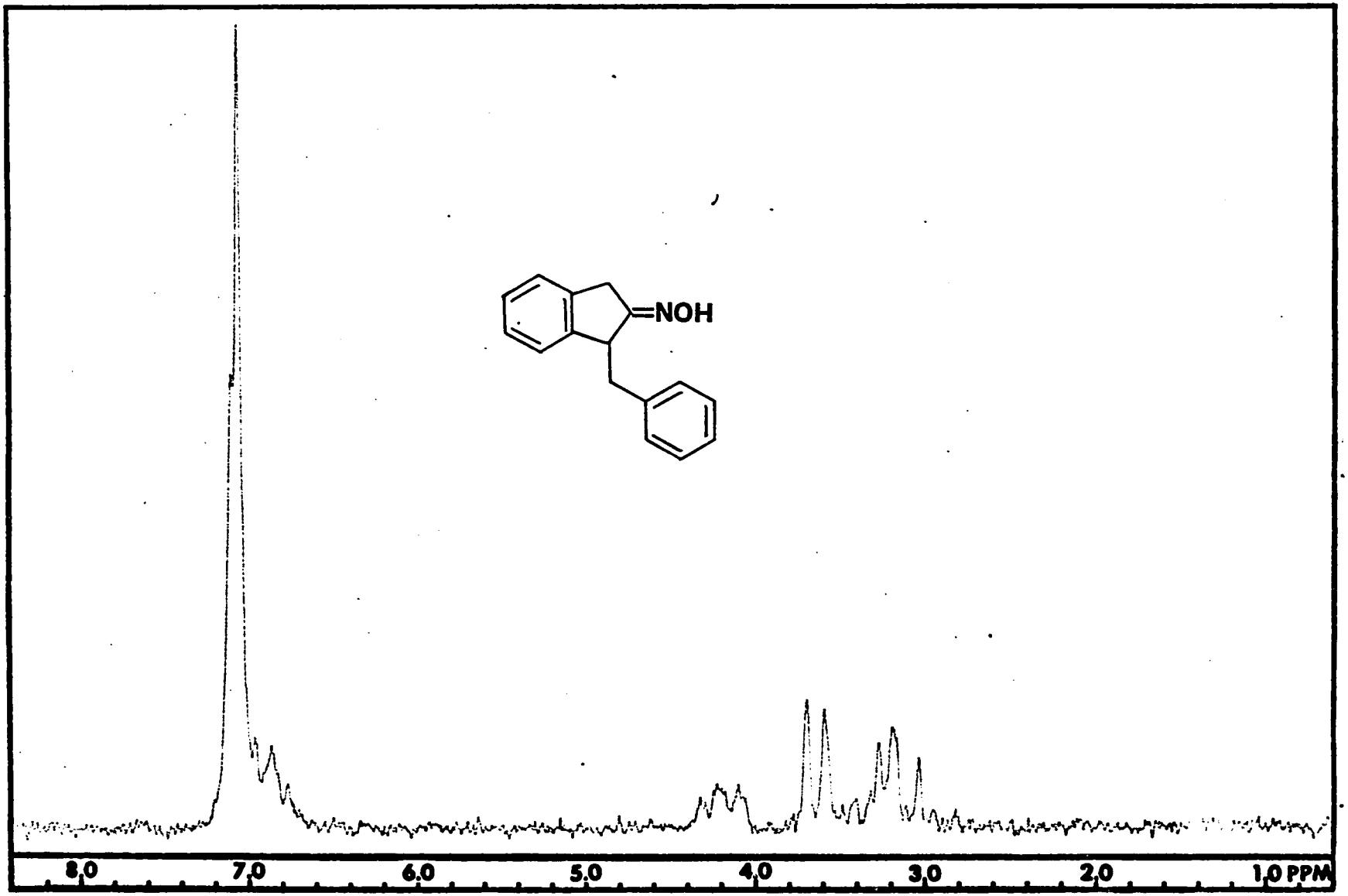
B-42. 2,3-Dimethoxy-N-(4'-nitrobenzyl)pavinane (130).



B-43. 2,3-Dimethoxy-N-(2',6'-dichlorobenzyl)pavinane (131).



B-44. 14-Methyl-6,7,12,13-tetrahydro-6,12-imino-5H-benzo[5,6]cyclooct[1,2-b]indole (152).



B-45. 1-Benzyl-2-indanonoxime (146).

BIOGRAPHICAL DATA

Name: David Allan Walsh

Date of Birth: August 3, 1945

Place of Birth: Schenectady, New York

Secondary Education:

Guilderland Central High School
Guilderland Center, New York

Collegiate Institutions Attended:

	Dates	Degree
Clarkson College of Technology Potsdam, New York	1963-1967	B.S.
University of New Hampshire Durham, New Hampshire	1968	M.S.

Publications:

"Conformation Studies of Nitrogen Heterocycles", with R. E. Lyle and J. J. Thomas, Conformational Analysis, G. Chiurdoglu, Ed., Academic Press, New York, 1971, pp 157-164.

"Intramolecular Charge Transfer Interactions in 1-Benzyl-1,2,3,4-tetrahydroisoquinolines", with R. E. Lyle, Abstracts, 4th Northeast Regional Meeting of the American Chemical Society, Hartford, Conn., Oct 1972, No. 83.

"An Improved Method for the Synthesis of Pavinane Derivatives", with R. E. Lyle, Tetrahedron Lett., 000 (1973) in press.

"A New Synthesis of 1,4-Dihydro-3-[2H]isoquinolone", with R. E. Lyle, submitted to Synthesis.

"A Novel Synthesis of the [4H]-1-oxa-3-azonia-2-boratanaphthalene Ring System", with R. E. Lyle, submitted to J. Organometal. Chem.